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Rec'd PC TO 08 AUG 2005

10/544899

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
10 September 2004 (10.09.2004)

PCT

(10) International Publication Number
WO 2004/075840 A2

(51) International Patent Classification[7]: A61K

(21) International Application Number: PCT/US2004/005199

(22) International Filing Date: 20 February 2004 (20.02.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/450,811 25 February 2003 (25.02.2003) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

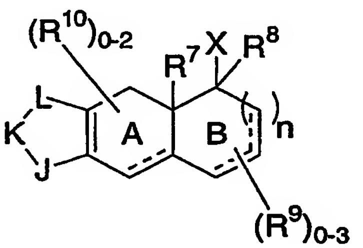
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2004/075840 A2

(54) Title: SELECTIVE NON-STEROIDAL GLUCOCORTICOID RECEPTOR MODULATORS

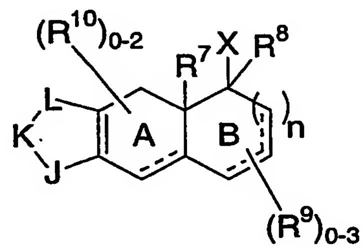


(I)

(57) Abstract: The present invention encompasses compounds of Formula (I) or pharmaceutically acceptable salts or hydrates thereof, which are useful as novel non-steroidal selective glucocorticoid receptor modulators for treating a variety of autoimmune and inflammatory diseases or conditions, and possess advantages over steroidal glucocorticoid ligands with respect to undesireable side-effects, efficacy, toxicity and/or metabolism. Pharmaceutical compositions and methods of use are also included.

SUMMARY OF THE INVENTION

The present invention encompasses compounds of Formula I:

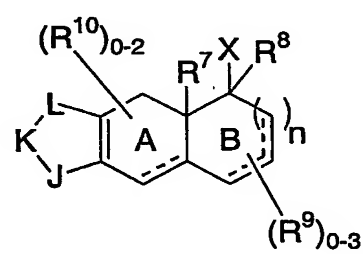


I

or pharmaceutically acceptable salts or hydrates thereof, which are useful as novel non-steroidal selective glucocorticoid receptor modulators for treating a variety of autoimmune and inflammatory diseases or conditions, and possess advantages over steroidal glucocorticoid ligands with respect to undesireable side-effects, efficacy, toxicity and/or metabolism. Pharmaceutical compositions and methods of use are also included.

DETAILED DESCRIPTION OF THE INVENTION

The present invention encompasses a compound represented by Formula I:



I

or a pharmaceutically acceptable salt or hydrate thereof, wherein:

n is 0, 1 or 2;

J is selected from NR^1 or $C(R^1)(R^2)$;

K is selected from NR^3 or $C(R^3)(R^4)$;

L is selected from NR^5 or $C(R^5)(R^6)$;

X is selected from the group consisting of:-OR^a, -N(R^b)-Y-R^c or -S(O)$_j$-R^d, wherein:

Y is selected from a bond, –C(O)-, –C(O)–O–, wherein the point of attachment of the "–O–" group is to R^c forming an alkoxy moiety, -S(O)$_2$- and -C(O)-N(R^{12})-, wherein the point of attachment of the nitrogen group is to R^c, and

j is independently 0, 1 or 2,

R^a, R^b, R^c, R^d and R^8 are each independently selected from the group consisting of:

(1) hydrogen, except that R^d is not hydrogen and R^c is hydrogen only when Y is a bond or -C(O)-N(R^{12})-,
(2) C_{1-6}alkyl,
(3) C_{2-6}alkenyl,
(4) C_{2-6}alkynyl,
(5) C_{3-6}cycloalkyl,
(6) aryl,
(7) aralkyl,
(8) HET^1,
(9) -C_{1-6}alkyl-HET^2,
(10) aralkenyl,
(11) aralkynyl and
(12) arylsulfonylalkyl,

wherein items (2) to (5) above and the alkyl portions of items (7), (9) and (12) above and the alkenyl portion of item (10) above and the alkynyl portion of item (11) above are optionally substituted from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of: halo, oxo, OR^{11}, N(R^{12})$_2$, C_{3-6}cycloalkyl and C_{1-4}alkyl-S(O)$_m$-, wherein m is 0, 1 or 2, and

wherein items (6) and (8) above and the aryl portion of items (7), (10), (11) and (12) above and the HET^2 portion of item (9) above are optionally substituted from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of:

(a) halo,
(b) OR^{11},
(c) N(R^{12})$_2$,

(d) C_{1-6}alkyl,
(e) C_{2-6}alkenyl,
(f) C_{2-6}akynyl,
(g) C_{1-6}alkyl-$S(O)_p$-, wherein p is 0, 1 or 2,
(h) aryl,
(i) aryl-$S(O)_q$-, wherein q is 0, 1 or 2,
(j) HET^3,
(k) aralkyl,
(l) aroyl,
(m) aryloxy,
(n) aralkoxy and
(o) CN,

wherein items (d) to (g) above and the alkyl portions of item (k) above are optionally substituted from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of: halo, OR^{11} and $N(R^{12})_2$, and

wherein items (h), (i), (j), (l) and (m) above and the aryl portions of items (k) and (n) above are optionally substituted from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of: halo, OR^{12} and C_{1-4}alkyl,

R^1, R^2, R^3, R^4, R^5 and R^6 are each independently selected from the group consisting of:
(1) hydrogen,
(2) halo,
(3) C_{1-6}alkyl,
(4) C_{2-6}alkenyl,
(5) C_{2-6}akynyl,
(6) C_{3-6}cycloalkyl,
(7) C_{1-6}alkoxy,
(8) C_{1-6}alkyl-$S(O)_r$-, wherein r is 0, 1 or 2,
(9) aryl,
(10) aralkyl,
(11) HET^4 and
(12) -C_{1-6}alkyl-HET^5,

wherein items (3) to (8) above and the alkyl portions of items (10) and (12) above are optionally substituted from one up to the maximum number of substitutable positions with a substituent

independently selected from the group consisting of: halo, OR^{11}, $N(R^{12})_2$ and C_{1-6}alkyl-$S(O)_s$-, wherein s is 0, 1 or 2; and

wherein items (9) and (11) and the aryl portion of items (10) and the HET portion of item (12) are optionally substituted from one up to the maximum number of substituable positions with a substituent independently selected from the group consisting of:

(a) halo,
(b) OR^{11},
(c) $N(R^{12})_2$,
(d) C_{1-6}alkyl,
(e) C_{2-6}alkenyl,
(f) C_{2-6}akynyl and
(g) C_{1-6}alkyl-$S(O)_t$-, wherein t is 0, 1 or 2,

wherein items (d) to (g) above are optionally substituted with from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of: halo, OR^{11} and $N(R^{12})_2$,

or R^1 and R^3 or R^3 and R^5 may be joined together to form a double bond;

R^7 is selected from the group consisting of:

(1) hydrogen,
(2) OR^{11},
(3) C_{1-4}alkyl,
(4) aryl and
(5) aralkyl,

wherein item (3) above and the alkyl portion of item (5) above are optionally substituted with from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of: halo, OR^{11} and $N(R^{12})_2$, and

wherein item (4) above and the aryl portion of item (5) above are optionally substituted with from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of:

(a) halo,
(b) OR^{11},
(c) $N(R^{12})_2$,

(d) C_{1-6}alkyl,

(e) C_{2-6}alkenyl and

(f) C_{2-6}akynyl,

wherein items (d) to (f) above are optionally substituted with from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of: halo, OR^{11} and $N(R^{12})_2$;

each R^9 and R^{10} is independently selected from the group consisting of:

(1) halo,

(2) C_{1-6}alkyl,

(3) C_{2-6}alkenyl,

(4) C_{1-6}alkoxy and

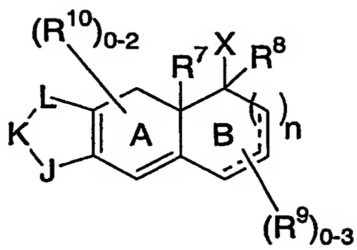
(5) hydroxy,

wherein items (2) to (4) above are optionally substituted from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of: halo, OR^{12}, $N(R^{11})_2$ and C_{1-6}alkyl-$S(O)_u$-, wherein u is 0, 1 or 2;

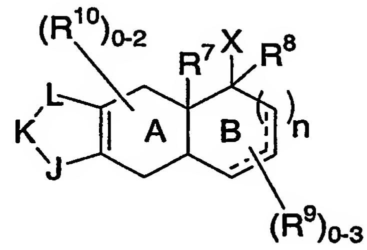
each R^{11} and R^{12} is independently selected from the group consisting of hydrogen and C_{1-4}alkyl, optionally substituted from one up to the maximum number of substitutable positions with halo; and

HET^1, HET^2, HET^3, HET^4 and HET^5 are each independently selected from the group of heterocycles consisting of: benzimidazolyl, benzofuranyl, benzopyrazolyl, benzotriazolyl, benzothiophenyl, benzoxazolyl, carbazolyl, carbolinyl, cinnolinyl, furanyl, imidazolyl, indolinyl, indolyl, indolazinyl, indazolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthyridinyl, oxadiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridopyridinyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, quinazolinyl, quinolyl, quinoxalinyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, azetidinyl, 1,4-dioxanyl, hexahydroazepinyl, piperazinyl, piperidinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, dihydrobenzimidazolyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, dihydrobenzoxazolyl, dihydrofuranyl, dihydroimidazolyl, dihydroindolyl, dihydroisooxazolyl, dihydroisothiazolyl, dihydrooxadiazolyl, dihydrooxazolyl, dihydropyrazinyl, dihydropyrazolyl, dihydropyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dihydroquinolinyl, dihydrotetrazolyl, dihydrothiadiazolyl, dihydrothiazolyl, dihydrothienyl, dihydrotriazolyl, dihydroazetidinyl, methylenedioxybenzoyl, tetrahydrofuranyl, and tetrahydrothienyl.

The optional double bond shown in ring A of the compound of Formula I is depicted as a dotted line and means that the double bond may or may not be present as shown below:

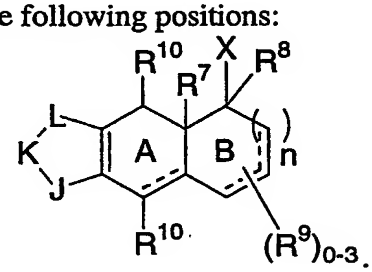


optional double bond is present in ring A



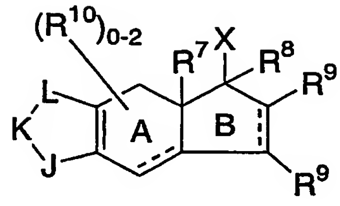
optional double bond is not present in ring A .

The substituent R^{10} in Formula I may or may not be present. When present, one or two R^{10} groups may occupy the following positions:

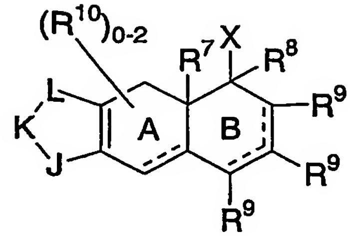


Two R^{10} groups may reside on the same carbon atom.

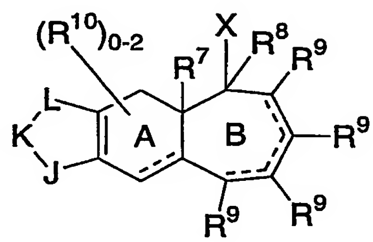
The substituent R^9 in Formula I may or may not be present. When present, one, two or three R^9 groups may occupy the following positions:



n=0



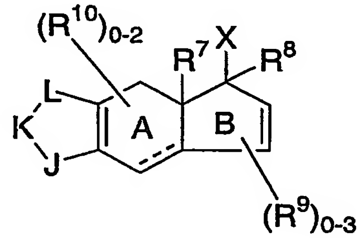
n=1



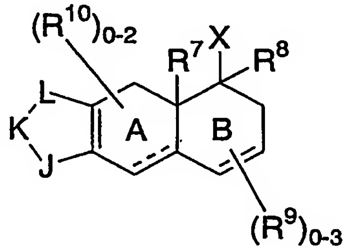
n=2

Two R^9 groups may reside on the same carbon atom.

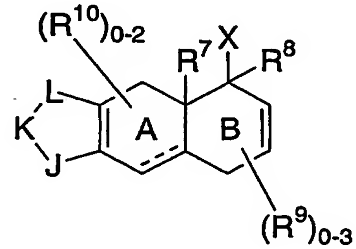
The optional double bonds show in ring B of the compound of Formula I may occupy the following positions:



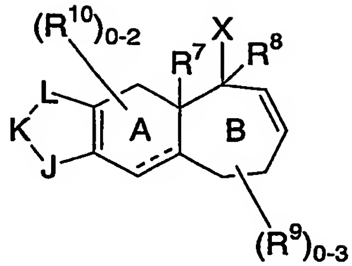
n=0



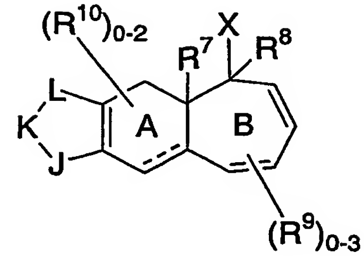
n=1



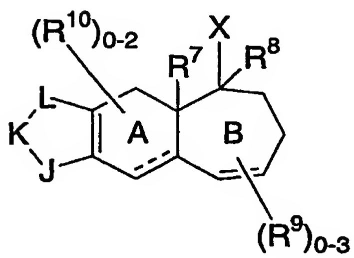
n=1



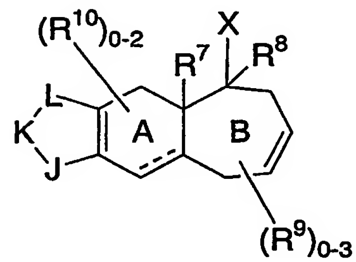
n=2



n=2

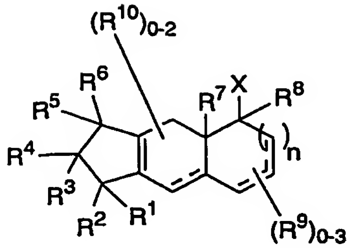
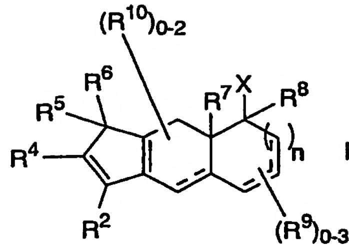
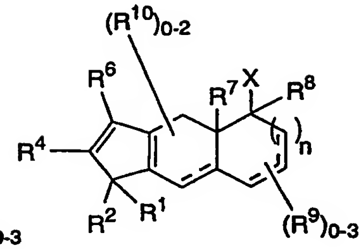
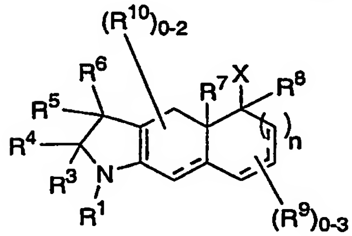
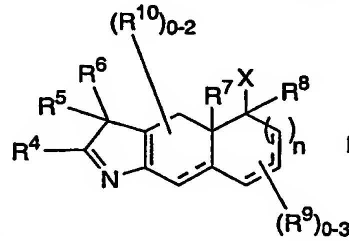
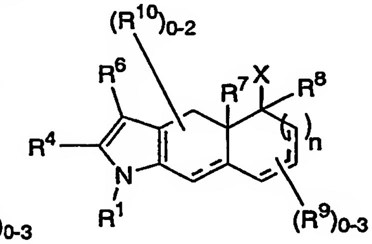
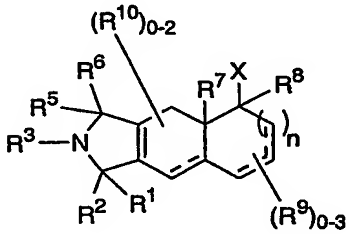
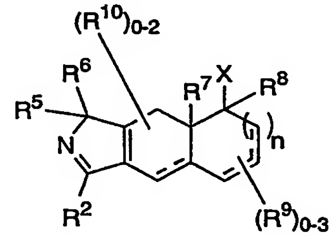
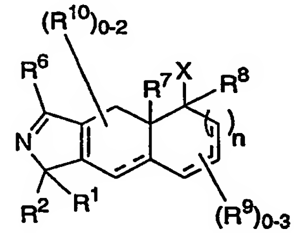
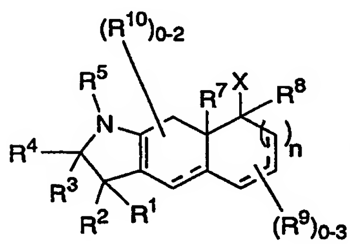
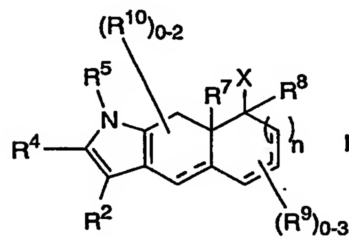
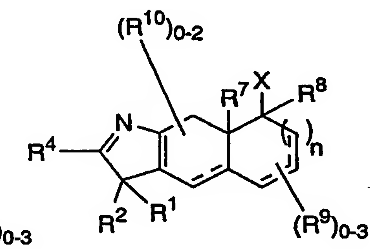
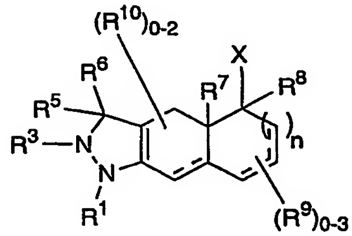
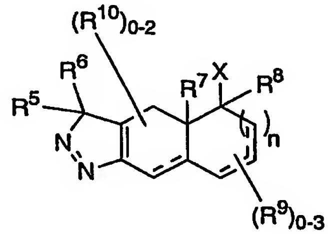
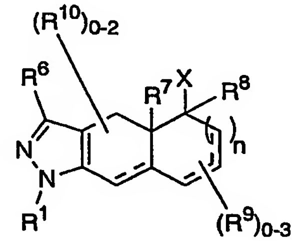


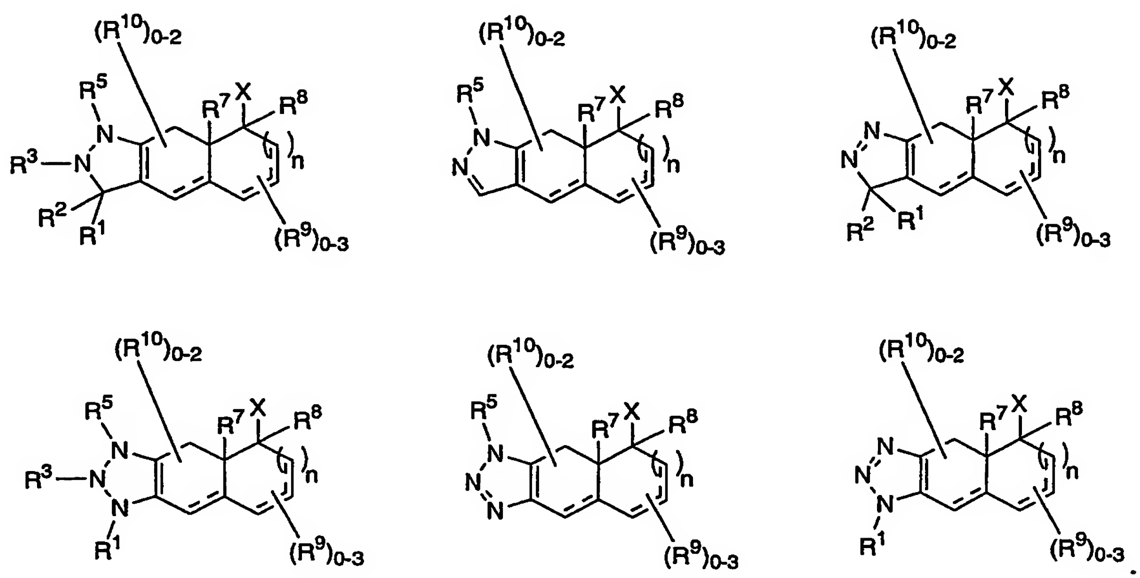
n=2



n=2

J, K and L as defined in Formula I mean, for example, the following structures:



An embodiment of the invention encompasses a compound of Formula I wherein:

J is NR^1;

K is NR^3;

L is $C(R^5)(R^6)$; and

R^3 and R^5 are joined together to form a double bond.

Another embodiment of the invention encompasses a compound of Formula I wherein the optional double bond shown in ring A of the compound of Formula I is present.

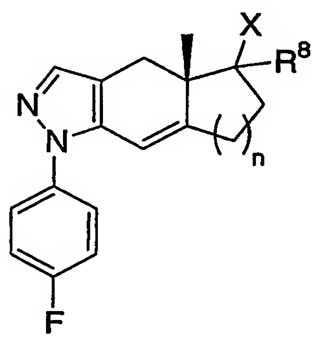
Another embodiment of the invention encompasses a compound of Formula I wherein X is $-OR^a$.

Another embodiment of the invention encompasses a compound of Formula I wherein X is $-N(R^b)-Y-R^c$, wherein Y is selected from $-C(O)-$, $-C(O)-O-$, wherein the point of attachment of the "–O–" group is to R^c forming an alkoxy moiety, $-S(O)_2-$ and $-C(O)-N(R^{12})-$, wherein the point of attachment of the nitrogen group is to R^c.

Another embodiment of the invention encompasses a compound of Formula I wherein X is $-S(O)_j-R^d$.

Another embodiment of the invention encompasses a compound of Formula I wherein n is 0 and the optional double bonds shown in ring B are not present.

An embodiment of the invention encompasses a compound of Formula II:



II

or a pharmaceutically acceptable salt or hydrate thereof, wherein:

X is selected from the group consisting of:-OR^a, -N(R^b)-Y-R^c, -S(O)$_j$-R^d, wherein:

Y is selected from a bond, –C(O)-, –C(O)–O–, wherein the point of attachment of the "–O–" group is to R^c forming an alkoxy moiety, -S(O)$_2$- and -C(O)-N(R^{12})-, wherein the point of attachment of the nitrogen group is to R^c, and

j is 0, 1 or 2,

n is 1 or 2,

R^a, R^b, R^c, R^d and R^8 are each independently selected from the group consisting of:

(1) hydrogen, except that R^d is not hydrogen and R^c is hydrogen only when Y is a bond or -C(O)-N(R^{12})-,

(2) C_{1-6}alkyl,

(3) C_{2-6}alkenyl,

(4) C_{2-6}akynyl,

(5) C_{3-6}cycloalkyl,

(6) aryl,

(7) aralkyl,

(8) HET^1,

(9) -C_{1-6}alkyl-HET^2,

(10) aralkenyl,

(11) aralkynyl and

(12) arylsulfonylalkyl,

wherein items (2) to (5) above and the alkyl portions of items (7), (9) and (12) above and the alkenyl portion of item (10) above and the alkynyl portion of item (11) above are optionally substituted with oxo and optionally substituted with one to three substituents independently selected from the group consisting of: halo, OR^{11}, $N(R^{12})_2$, C_{3-6}cycloalkyl and C_{1-4}alkyl-$S(O)_m$-, wherein m is 0, 1 or 2, and

wherein items (6) and (8) above and the aryl portion of items (7), (10), (11) and (12) above and the HET^2 portion of item (9) above are optionally substituted with one to five substituents independently selected from the group consisting of:

(a) halo,

(b) OR^{11},

(c) $N(R^{12})_2$,

(d) C_{1-6}alkyl,

(e) C_{2-6}alkenyl,

(f) C_{2-6}akynyl,

(g) C_{1-6}alkyl-$S(O)_p$-, wherein p is 0, 1 or 2,

(h) aryl,

(i) aryl-$S(O)_q$-, wherein q is 0, 1 or 2,

(j) HET^3,

(k) aralkyl,

(l) aroyl,

(m) aryloxy,

(n) aralkoxy and

(o) CN,

wherein items (d) to (g) above and the alkyl portions of item (k) above are optionally substituted with one to three substituents independently selected from the group consisting of: halo, OR^{11} and $N(R^{12})_2$, and

wherein items (h), (i), (j), (l) and (m) above and the aryl portions of items (k) and (n) above are optionally substituted with one to three substituents independently selected from the group consisting of: halo, OR^{12} and C_{1-4}alkyl,

each R^{11} and R^{12} is independently selected from the group consisting of hydrogen and C_{1-4}alkyl, optionally substituted with 1 to 3 halo groups; and

HET^1, HET^2 and HET^3 are each independently selected from the group of heterocycles consisting of: benzimidazolyl, benzofuranyl, benzopyrazolyl, benzotriazolyl, benzothiophenyl, benzoxazolyl, carbazolyl, carbolinyl, cinnolinyl, furanyl, imidazolyl, indolinyl, indolyl, indolazinyl, indazolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthyridinyl, oxadiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridopyridinyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, quinazolinyl, quinolyl, quinoxalinyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, azetidinyl, 1,4-dioxanyl, hexahydroazepinyl, piperazinyl, piperidinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, dihydrobenzimidazolyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, dihydrobenzoxazolyl, dihydrofuranyl, dihydroimidazolyl, dihydroindolyl, dihydroisooxazolyl, dihydroisothiazolyl, dihydrooxadiazolyl, dihydrooxazolyl, dihydropyrazinyl, dihydropyrazolyl, dihydropyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dihydroquinolinyl, dihydrotetrazolyl, dihydrothiadiazolyl, dihydrothiazolyl, dihydrothienyl, dihydrotriazolyl, dihydroazetidinyl, methylenedioxybenzoyl, tetrahydrofuranyl, and tetrahydrothienyl.

Another embodiment of the invention encompasses a compound of Formula II wherein

X is $-OR^a$

n is 1, and

R^a is selected from the group consisting of:

(1) hydrogen,
(2) acetyl,
(3) benzyl,
(4) C_{1-6}alkyl,
(5) C_{2-6}alkenyl,
(6) C_{2-6}alkynyl and
(7) C_{3-6}cycloalkyl,

R^8 is selected from the group consisting of:

(1) hydrogen,
(2) C_{1-6}alkyl,

(3) C_{2-6}alkenyl,
(4) C_{2-6}akynyl,
(5) C_{3-6}cycloalkyl,
(6) aryl,
(7) aralkyl,
(8) HET^1,
(9) $-C_{1-6}$alkyl-HET^2,
(10) aralkenyl,
(11) aralkynyl, and
(12) arylsulfonylalkyl

wherein items (2) to (5) above and the alkyl portions of items (7), (9) and (12) above and the alkenyl portion of item (10) above and the alkynyl portion of item (11) above are optionally substituted with oxo and optionally substituted with one to three substituents independently selected from the group consisting of: halo, OR^{11} and C_{3-6}cycloalkyl,

wherein items (6) and (8) above and aryl portion of items (7), (10), (11) and (12) above and the HET^2 portion of item (9) above are optionally substituted with one to five substituents independently selected from the group consisting of:

(a) halo,
(b) C_{1-6}alkyl,
(c) C1-4alkoxy and
(d) aryl,

R^{11} is selected from the group consisting of hydrogen and C_{1-4}alkyl, optionally substituted with 1 to 3 halo groups; and

HET^1 and HET^2 are each independently selected from the group of heterocycles consisting of: benzimidazolyl, benzofuranyl, benzopyrazolyl, benzotriazolyl, benzothiophenyl, benzoxazolyl, carbazolyl, carbolinyl, cinnolinyl, furanyl, imidazolyl, indolinyl, indolyl, indolazinyl, indazolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthyridinyl, oxadiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridopyridinyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, quinazolinyl, quinolyl, quinoxalinyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, azetidinyl, 1,4-dioxanyl, hexahydroazepinyl, piperazinyl, piperidinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, dihydrobenzimidazolyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, dihydrobenzoxazolyl, dihydrofuranyl, dihydroimidazolyl, dihydroindolyl, dihydroisooxazolyl,

dihydroisothiazolyl, dihydrooxadiazolyl, dihydrooxazolyl, dihydropyrazinyl, dihydropyrazolyl, dihydropyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dihydroquinolinyl, dihydrotetrazolyl, dihydrothiadiazolyl, dihydrothiazolyl, dihydrothienyl, dihydrotriazolyl, dihydroazetidinyl, methylenedioxybenzoyl, tetrahydrofuranyl, and tetrahydrothienyl.

Within this embodiment is encompassed a compound of Formula II wherein:

R^8 is selected from the group consisting of:

(1) hydrogen,
(2) C_{1-6}alkyl,
(3) C_{2-6}alkenyl,
(4) C_{2-6}akynyl,
(5) C_{3-6}cycloalkyl,
(6) phenyl or naphthyl,
(7) benzyl or phenethyl,
(8) benzothiophene,
(9) phenylethenyl,
(10) phenylethynyl, and
(11) phenylsulfonylmethyl,

wherein items (2) to (5) above are optionally substituted with one to three substituents independently selected from the group consisting of: halo, OR^{11} and C_{3-6}cycloalkyl,

wherein item (6) above and the phenyl portions of items (7), (9), (10) and (11) above are optionally substituted with one to five substituents independently selected from the group consisting of:

(a) halo,
(b) C_{1-6}alkyl,
(c) C_{1-4}alkoxy and
(d) phenyl.

Another embodiment of the invention encompasses a compound of Formula II wherein:

X is $-N(R^b)-Y-R^c$, wherein:

Y is selected from –C(O)-, –C(O)–O–, wherein the point of attachment of the "–O–" group is to R^c forming an alkoxy moiety, $-S(O)_2-$ and $-C(O)-N(R^{12})-$, wherein the point of attachment of the nitrogen group is to R^c, and

n is 1,

R^8 is hydrogen, and

R^b and R^c are each independently selected from the group consisting of:

(1) hydrogen, except that R^c is not hydrogen,
(2) C_{1-6}alkyl,
(3) C_{2-6}alkenyl,
(4) C_{2-6}akynyl,
(5) C_{3-6}cycloalkyl,
(6) aryl,
(7) aralkyl,
(8) HET^1,
(9) $-C_{1-6}$alkyl-HET^2,
(10) aralkenyl,
(11) aralkynyl and
(12) arylsulfonylalkyl,

wherein items (2) to (5) above and the alkyl portions of items (7), (9) and (12) above and the alkenyl portion of item (10) above and the alkynyl portion of item (11) above are optionally substituted with oxo and optionally substituted with with one to three substituents independently selected from the group consisting of: halo, OR^{11}, $N(R^{12})_2$, C_{3-6}cycloalkyl and C_{1-4}alkyl-$S(O)_m$-, wherein m is 0, 1 or 2, and

wherein items (6) and (8) above and the aryl portion of items (7), (10), (11) and (12) above and the HET^2 portion of item (9) above are optionally substituted with one to five substituents independently selected from the group consisting of:

(a) halo,
(b) OR^{11},
(c) $N(R^{12})_2$,
(d) C_{1-6}alkyl,
(e) C_{2-6}alkenyl,

(f) C_{2-6}akynyl,

(g) C_{1-6}alkyl-$S(O)_p$-, wherein p is 0, 1 or 2,

(h) aryl,

(i) aryl-$S(O)_q$-, wherein q is 0, 1 or 2,

(j) HET^3,

(k) aralkyl,

(l) aroyl,

(m) aryloxy,

(n) aralkoxy and

(o) CN,

wherein items (d) to (g) above and the alkyl portions of item (k) above are optionally substituted with one to three substituents independently selected from the group consisting of: halo, OR^{11} and $N(R^{12})_2$, and

wherein items (h), (i), (j), (l) and (m) above and the aryl portions of items (k) and (n) above are optionally substituted with one to three substituents independently selected from the group consisting of: halo, OR^{12} and C_{1-4}alkyl,

each R^{11} and R^{12} is independently selected from the group consisting of hydrogen and C_{1-4}alkyl, optionally substituted with 1 to 3 halo groups; and

HET^1, HET^2 and HET^3 are each independently selected from the group of heterocycles consisting of: benzimidazolyl, benzofuranyl, benzopyrazolyl, benzotriazolyl, benzothiophenyl, benzoxazolyl, carbazolyl, carbolinyl, cinnolinyl, furanyl, imidazolyl, indolinyl, indolyl, indolazinyl, indazolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthyridinyl, oxadiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridopyridinyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, quinazolinyl, quinolyl, quinoxalinyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, azetidinyl, 1,4-dioxanyl, hexahydroazepinyl, piperazinyl, piperidinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, dihydrobenzimidazolyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, dihydrobenzoxazolyl, dihydrofuranyl, dihydroimidazolyl, dihydroindolyl, dihydroisooxazolyl, dihydroisothiazolyl, dihydrooxadiazolyl, dihydrooxazolyl, dihydropyrazinyl, dihydropyrazolyl, dihydropyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dihydroquinolinyl, dihydrotetrazolyl, dihydrothiadiazolyl, dihydrothiazolyl, dihydrothienyl, dihydrotriazolyl, dihydroazetidinyl, methylenedioxybenzoyl, tetrahydrofuranyl, and tetrahydrothienyl.

Within this ebodiment is encompassed a compound of Formula II wherein:

R^b and R^c are each independently selected from the group consisting of:

(1) hydrogen, except that R^c is hydrogen only when Y is a bond or -C(O)-N(R^{12})-,

(2) C_{1-6}alkyl,
(3) C_{2-6}alkenyl,
(4) C_{2-6}akynyl,
(5) C_{3-6}cycloalkyl,
(6) aryl,
(7) aralkyl,
(8) HET^1,
(9) -C_{1-6}alkyl-HET^2,
(10) aralkenyl, and
(11) aralkynyl,

wherein items (2) to (5) above are optionally substituted with 1-3 halo groups, and

wherein items (6) and (8) and aryl portion of items (7), (10) and (11) above and the HET^2 portion of item (9) above are optionally substituted with one to five substituents independently selected from the group consisting of:

(a) halo,
(b) C_{1-4}alkyl, optionally substituted with 1-3 halo groups, and
(c) C_{1-4}alkylthio,

HET^1 and HET^2 are each independently selected from the group of heterocycles consisting of: benzimidazolyl, benzofuranyl, benzopyrazolyl, benzotriazolyl, benzothiophenyl, benzoxazolyl, carbazolyl, carbolinyl, cinnolinyl, furanyl, imidazolyl, indolinyl, indolyl, indolazinyl, indazolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthyridinyl, oxadiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridopyridinyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, quinazolinyl, quinolyl, quinoxalinyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, azetidinyl, 1,4-dioxanyl, hexahydroazepinyl, piperazinyl, piperidinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, dihydrobenzimidazolyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, dihydrobenzoxazolyl, dihydrofuranyl, dihydroimidazolyl, dihydroindolyl, dihydroisooxazolyl, dihydroisothiazolyl, dihydrooxadiazolyl, dihydrooxazolyl, dihydropyrazinyl, dihydropyrazolyl, dihydropyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dihydroquinolinyl, dihydrotetrazolyl,

dihydrothiadiazolyl, dihydrothiazolyl, dihydrothienyl, dihydrotriazolyl, dihydroazetidinyl, methylenedioxybenzoyl, tetrahydrofuranyl, and tetrahydrothienyl.

Also within this embodiment is encompassed a compound of Formula II wherein:

R^b is selected from the group consisting of: hydrogen and C_{1-4}alkyl, and

R^c is selected from the group consisting of:

(1) C_{1-4}alkyl,

(2) phenyl or benzyl, each optionally substituted with 1 to 5 groups independently selected from fluoro, chloro and trifluoromethyl,

(3) naphthyl,

(4) thiopheneyl,

(5) pyridyl,

(6) isoquinolyl,

(7) pyrimidyl and

(8) pyrazyl,

wherein items (4) to (8) above are optionally substitited with 1 to 5 groups independently selected from fluoro, chloro, methyl,methylthio and trifluoromethyl.

Also within this embodiment of the invention is encompassed a compound of Formula II wherein R^c is phenyl, optionally substituted with 1 to 5 groups independently selected from fluoro, chloro and trifluoromethyl.

Another embodiment of the invention encompasses a compound of Formula II wherein:

X is $-S(O)_j-R^d$, wherein j is 0, 1 or 2,

n is 1,

R^8 is hydrogen, and

R^d is selected from the group consisting of:

(1) C_{1-6}alkyl,

(2) C_{2-6}alkenyl,

(3) C_{2-6}akynyl,

(4) C_{3-6}cycloalkyl,

(5) aryl,
(6) aralkyl,
(7) HET^1,
(8) $-C_{1-6}$alkyl-HET^2,
(9) aralkenyl, and
(10) aralkynyl,

wherein items (1) to (4) above are optionally substituted with 1-3 halo groups, and

wherein items (5) and (7) and aryl portion of items (6), (9) and (10) above and the HET^2 portion of item (8) above are optionally substituted with one to five substituents independently selected from the group consisting of:

(a) halo,
(b) C_{1-4}alkyl, optionally substituted with 1-3 halo groups, and
(c) C_{1-4}alkylthio, and

HET^1 and HET^2 are each independently selected from the group of heterocycles consisting of: benzimidazolyl, benzofuranyl, benzopyrazolyl, benzotriazolyl, benzothiophenyl, benzoxazolyl, carbazolyl, carbolinyl, cinnolinyl, furanyl, imidazolyl, indolinyl, indolyl, indolazinyl, indazolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthyridinyl, oxadiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridopyridinyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, quinazolinyl, quinolyl, quinoxalinyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, azetidinyl, 1,4-dioxanyl, hexahydroazepinyl, piperazinyl, piperidinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, dihydrobenzimidazolyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, dihydrobenzoxazolyl, dihydrofuranyl, dihydroimidazolyl, dihydroindolyl, dihydroisooxazolyl, dihydroisothiazolyl, dihydrooxadiazolyl, dihydrooxazolyl, dihydropyrazinyl, dihydropyrazolyl, dihydropyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dihydroquinolinyl, dihydrotetrazolyl, dihydrothiadiazolyl, dihydrothiazolyl, dihydrothienyl, dihydrotriazolyl, dihydroazetidinyl, methylenedioxybenzoyl, tetrahydrofuranyl, and tetrahydrothienyl.

Within this embodiment is encompassed a compound of Formula II wherein

R^d is phenyl, optionally substituted with 1 to 5 groups independently selected from fluoro, chloro and trifluoromethyl.

Another embodiment of the invention encompasses a pharmaceutical composition comprising a compound of Formula I in combination with a pharmaceutically acceptable carrier.

Another embodiment of the invention encompasses a method for treating a glucocorticoid receptor mediated disease or condition in a mammalian patient in need of such treatment comprising administering the patient a compound of Formula I in an amount that is effective for treating the glucocorticoid receptor mediated disease or condition.

Within this embodiment is encompassed the above method wherein the glucocorticoid receptor mediated disease or condition is selected from the group consisting of: tissue rejection, leukemias, lymphomas, Cushing's syndrome, acute adrenal insufficiency, congenital adrenal hyperplasia, rheumatic fever, polyarteritis nodosa, granulomatous polyarteritis, inhibition of myeloid cell lines, immune proliferation/apoptosis, HPA axis suppression and regulation, hypercortisolemia, stroke and spinal cord injury, hypercalcemia, hyperglycemia, acute adrenal insufficiency, chronic primary adrenal insufficiency, secondary adrenal insufficiency, congenital adrenal hyperplasia, cerebral edema, thrombocytopenia, Little's syndrome, obesity, metabolic syndrome, inflammatory bowel disease, systemic lupus erythematosus, polyartitis nodosa, Wegener's granulomatosis, giant cell arteritis, rheumatoid arthritis, juvenile rheumatoid arthritis, uveitis, hay fever, allergic rhinitis, urticaria, angioneurotic edema, chronic obstructive pulmonary disease, asthma, tendonitis, bursitis, Crohn's disease, ulcerative colitis, autoimmune chronic active hepatitis, organ transplantation, hepatitis, cirrhosis, inflammatory scalp alopecia, panniculitis, psoriasis, discoid lupus erythematosus, inflamed cysts, atopic dermatitis, pyoderma gangrenosum, pemphigus vulgaris, buflous pemphigoid, systemic lupus erythematosus, dermatomyositis, herpes gestationis, eosinophilic fasciitis, relapsing polychondritis, inflammatory vasculitis, sarcoidosis, Sweet's disease, type I reactive leprosy, capillary hemangiomas, contact dermatitis, atopic dermatitis, lichen planus, exfoliative dermatitus, erythema nodosum, acne, hirsutism, toxic epidermal necrolysis, erythema multiform, cutaneous T-cell lymphoma, Human Immunodeficiency Virus (HIV), cell apoptosis, cancer, Kaposi's sarcoma, retinitis pigmentosa, cognitive performance, memory and learning enhancement, depression, addiction, mood disorders, chronic fatigue syndrome, schizophrenia, sleep disorders, and anxiety.

Another embodiment of the invention encompasses a method of selectively modulating the transactivation, transrepression, agonism and antagonism effects of the glucocorticoid receptor in a mammal comprising administering to the mammal a compound of Formula I in an amount that is effective to modulate the glucocorticoid receptor.

The invention is described using the following definitions unless otherwise indicated.

The term "halogen" or "halo" includes F, Cl, Br, and I.

The term "alkyl" means linear or branched structures and combinations thereof, having the indicated number of carbon atoms. Thus, for example, C_{1-6}alkyl includes methyl, ethyl, propyl, 2-propyl, s- and t-butyl, butyl, pentyl, hexyl, 1,1-dimethylethyl, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The term "alkoxy" means alkoxy groups of a straight, branched or cyclic configuration having the indicated number of carbon atoms. C_{1-6}alkoxy, for example, includes methoxy, ethoxy, propoxy, isopropoxy, and the like.

The term "alkylthio" means alkylthio groups having the indicated number of carbon atoms of a straight, branched or cyclic configuration. C_{1-6}alkylthio, for example, includes methylthio, propylthio, isopropylthio, and the like.

The term "alkenyl" means linear or branched structures and combinations thereof, of the indicated number of carbon atoms, having at least one carbon-to-carbon double bond, wherein hydrogen may be replaced by an additional carbon-to-carbon double bond. C_{2-6}alkenyl, for example, includes ethenyl, propenyl, 1-methylethenyl, butenyl and the like.

The term "alkynyl" means linear or branched structures and combinations thereof, of the indicated number of carbon atoms, having at least one carbon-to-carbon triple bond. C_{3-6}alkynyl, for example, includes , propenyl, 1-methylethenyl, butenyl and the like.

The term "cycloalkyl" means mono-, bi- or tri-cyclic structures, optionally combined with linear or branched structures, the indicated number of carbon atoms. Examples of cycloalkyl groups include cyclopropyl, cyclopentyl, cycloheptyl, adamantyl, cyclododecylmethyl, 2-ethyl-1- bicyclo[4.4.0]decyl, and the like.

The term "aryl" is defined as a mono- or bi-cyclic aromatic ring system and includes, for example, phenyl, naphthyl, and the like.

The term "aralkyl" means an alkyl group as defined above of 1 to 6 carbon atoms with an aryl group as defined above substituted for one of the alkyl hydrogen atoms, for example, benzyl and the like.

The term "aralkenyl" means an alkenyl group as defined above of 2 to 6 carbon atoms with an aryl group as defined above substituted for one of the alkenyl hydrogen atoms, for example, phenethenyl and the like.

The term "aralkynyl" means an alkynyl group as defined above of 2 to 6 carbon atoms with an aryl group as defined above substituted for one of the alkynyl hydrogen atoms, for example, phenethynyl and the like.

The term "aryloxy" means an aryl group as defined above attached to a molecule by an oxygen atom (aryl-O) and includes, for example, phenoxy, naphthoxy and the like.

The term "aralkoxy" means an aralkyl group as defined above attached to a molecule by an oxygen atom (aralkyl-O) and includes, for example, benzyloxy, and the like.

The term "arylthio" is defined as an aryl group as defined above attached to a molecule by an sulfur atom (aryl-S) and includes, for example, thiophenyoxy, thionaphthoxy and the like.

The term "aroyl" means an aryl group as defined above attached to a molecule by an carbonyl group (aryl-C(O)-) and includes, for example, benzoyl, naphthoyl and the like.

The term "aroyloxy" means an aroyl group as defined above attached to a molecule by an oxygen atom (aroyl-O) and includes, for example, benzoyloxy or benzoxy, naphthoyloxy and the like.

For all of the above definitions, each reference to a group is independent of all other references to the same group when referred to in the Specification. For example, if both R^1 and R^2 are aryl, the definitions of aryl are independent of each other and R^1 and R^2 may be different aryl groups, for example phenyl and naphthyl.

The term "arylsulfonylalkyl" means aryl as defined above linked to a sulfonyl group linked to an alkyl group as defined above of 1 to 6 carbon atoms, such as phenylsulfonylmethyl and the like.

The term "treating" encompasses not only treating a patient to relieve the patient of the signs and symptoms of the disease or condition but also prophylactically treating an asymptomatic patient to prevent the onset of the disease or condition or preventing, slowing or reversing the progression of the disease or condition. The term "amount effective for treating" is intended to mean that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, a system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician. The term also encompasses the amount of a pharmaceutical drug that will prevent or reduce the risk of occurrence of the biological or medical event that is sought to be prevented in a tissue, a system, animal or human by a researcher, veterinarian, medical doctor or other clinician.

The following abbreviations have the indicated meanings:

9-BBN	=	9-borabicyclo[3.3.1]nonane
BOP	=	benzotriazol-1-yloxy-tris(dimethylamino)-phosphonium hexafluorophosphate
Dess-Martin periodinane	=	[1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1*H*)-one]

dba	=	dibenzylideneacetone
DIEA	=	diisopropylethylamine (Hunig's base)
DMAC	=	*N,N*-dimethylacetamide
DMAP	=	4-(dimethylamino)pyridine
DME	=	ethylene glycol dimethylether
DMF	=	*N,N*-dimethylformamide
DMSO	=	dimethyl sulfoxide
dppf	=	1,1'-bis(diphenylphosphino)ferrocene
E	=	transoid
HMPA	=	hexamethylphosphoramide
HOBt	=	1-hydroxybenzotriazole
HPLC	=	high performance liquid chromatography
LCMS	=	tandem HPLC followed by MS
MS	=	mass spectrum (or mass spectroscopy)
MsCl	=	methanesulfonyl chloride
N	=	nitrogen-substituted
NBS	=	*N*-bromosuccinimide
NMR	=	nuclear magnetic resonance
NSAID	=	non-steroidal anti-inflammatory drug
TFA	=	trifluoroacetic acid
THF	=	tetrahydrofuran
TLC	=	thin layer chromatography
Z	=	cisoid

<u>Alkyl group abbreviations</u>

n	=	normal
Me	=	methyl
Et	=	ethyl
n-Pr	=	normal propyl
i-Pr	=	isopropyl
n-Bu	=	normal butyl
i-Bu	=	isobutyl
s-Bu	=	secondary butyl
t-Bu	=	(tert) or tertiary butyl
c-Pr	=	cyclopropyl

c-Bu	=	cyclobutyl
c-Pen	=	cyclopentyl
c-Hex	=	cyclohexyl

Some of the compounds described herein contain one or more asymmetric centers and may thus give rise to diastereomers and optical isomers. The present invention is meant to comprehend such possible diastereomers as well as their racemic and resolved, enantiomerically pure forms and pharmaceutically acceptable salts thereof.

Some of the compounds described herein contain olefinic double bonds, and unless specified otherwise, are meant to include both *E* and *Z* geometric isomers.

The pharmaceutical compositions of the present invention comprise a compound of Formula I as an active ingredient or a pharmaceutically acceptable salt, thereof, and may also contain a pharmaceutically acceptable carrier and optionally other therapeutic ingredients. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, *N,N'*-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, *N*-ethyl-morpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, para-toluenesulfonic acid, and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, and tartaric acids.

It will be understood that in the discussion of methods of treatment which follows, references to the compounds of Formula I are meant to also include the pharmaceutically acceptable salts.

The magnitude of prophylactic or therapeutic dose of a compound of Formula I will, of course, vary with the nature and the severity of the condition to be treated and with the particular compound of Formula I and its route of administration. It will also vary according to a variety of factors including the age, weight, general health, sex, diet, time of administration, rate of excretion, drug combination and response of the individual patient. In general, the daily dose from about 0.001 mg to about 100 mg per kg body weight of a mammal, preferably 0.01 mg to about 10 mg per kg. On the other hand, it may be necessary to use dosages outside these limits in some cases.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for oral administration to humans may contain from about 0.5 mg to about 5 g of active agent compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Dosage unit forms will generally contain from about 1 mg to about 2 g of an active ingredient, typically 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 800 mg, or 1000 mg. The "effective amount" for treatment refers to an optimal amount of drug or pharmaceutical agent which elicits the greatest index between desireable pharmacology and undesireable side-effects.

For the treatment of glucocorticoid receptor mediated diseases the compound of Formula I may be administered orally, topically, parenterally, by inhalation spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous, intravenous, intramuscular, intrasternal injection or infusion techniques. In addition to the treatment of warm-blooded animals such as mice, rats, horses, cattle, sheep, dogs, cats, etc., the compound of the invention is effective in the treatment of humans.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, solutions, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavouring agents, colouring agents and preserving agents in order to provide pharmaceutically elegant and

palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example, magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the technique described in the U.S. Patent 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for control release.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredients is mixed with water-miscible solvents such as propylene glycol, PEGs and ethanol, or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active material in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropyl methylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more colouring agents, one or more flavouring agents, and one or more sweetening agents, such as sucrose, saccharin or aspartame.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavouring

agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavouring and colouring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of an oil-in-water emulsion. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavouring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavouring and colouring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. Cosolvents such as ethanol, propylene glycol or polyethylene glycols may also be used. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds of Formula I may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ambient temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

For topical use, creams, ointments, gels, solutions or suspensions, etc., containing a compound of Formula I are employed. (For purposes of this application, topical application

shall include mouth washes and gargles.) Topical formulations may generally be comprised of a pharmaceutical carrier, cosolvent, emulsifier, penetration enhancer, preservative system, and emollient.

The ability of the compounds of Formula I to selectively modulate glucocorticoid receptors makes them useful for treating, preventing or reversing the progression of a variety of inflammatory and autoimmune diseases and conditions. Thus, the compounds of the present invention are useful to treat, prevent or ameliorate the following diseases or conditions: inflammation, tissue rejection, auto-immunity, various malianancies, such as leukemias and lymphomas, Cushing's syndrome, acute adrenal insufficiency, congenital adrenal hyperplasia, rheumatic fever, polyarteritis nodosa, granulomatous polyarteritis, inhibition of myeloid cell lines, immune proliferation/apoptosis, HPA axis suppression and regulation, hypercortisolemia, stroke and spinal cord injury, hypercalcemia, hypergylcemia, acute adrenal insufficiency, chronic primary adrenal insufficiency, secondary adrenal insufficiency, congenital adrenal hyperplasia, cerebral edema, thrombocytopenia, Little's syndrome, obesity and metabolic syndrome.

The compounds of the present invention are also useful for treating, preventing or reversing the progression of disease states involving systemic inflammation such as inflammatory bowel disease, systemic lupus erythematosus, polyartitis nodosa, Wegener's granulomatosis, giant cell arteritis, rheumatoid arthritis, juvenile rheumatoid arthritis, uveitis, hay fever, allergic rhinitis, urticaria, angioneurotic edema, chronic obstructive pulmonary disease, asthma, tendonitis, bursitis, Crohn's disease, ulcerative colitis, autoimmune chronic active hepatitis, organ transplantation, hepatitis, and cirrhosis.

The compounds of the present invention are useful for treating, preventing or reversing the progression of a variety of topical diseases such as inflammatory scalp alopecia, panniculitis, psoriasis, discoid lupus erythematosus, inflamed cysts, atopic dermatitis, pyoderma gangrenosum, pemphigus vulgaris, buflous pemphigoid, systemic lupus erythematosus, dermatomyositis, herpes gestationis, eosinophilic fasciitis, relapsing polychondritis, inflammatory vasculitis, sarcoidosis, Sweet's disease, type I reactive leprosy, capillary hemangiomas, contact dermatitis, atopic dermatitis, lichen planus, exfoliative dermatitus, erythema nodosum, acne, hirsutism, toxic epidermal necrolysis, erythema multiform, cutaneous T-cell lymphoma.

The compounds of the present invention are also useful in treating, preventing or reversing the progression of disease states associated with Human Immunodeficiency Virus (HIV), cell apoptosis, and cancer including, but not limited to, Kaposi's sarcoma, immune system activation and modulation, desensitization of inflammatory responses, IIL- I expression, natural killer cell development, lymphocytic leukemia, and treatment of retinitis pigmentosa. Cogitive

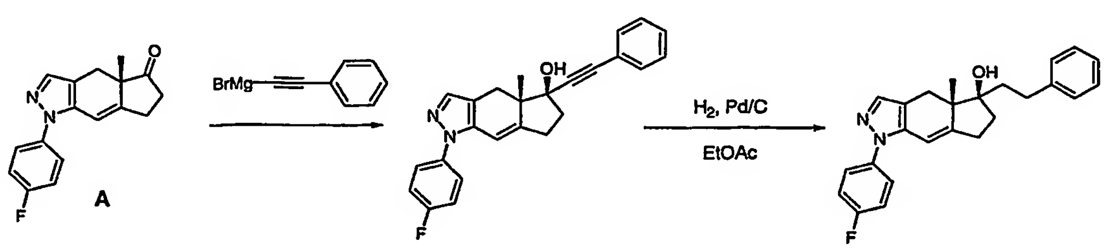
and behavioral processes are also susceptible to glucocorticoid therapy where antagonists would potentially be useful in the treatment of processes such as cognitive performance, memory and learning enhancement, depression, addiction, mood disorders, chronic fatigue syndrome, schizophrenia, stroke, sleep disorders, and anxiety.

The invention also encompasses a method for treating a glucocorticoid receptor mediated disease comprising concomitantly administering to a patient in need of such treatment a compound of Formula I and one or additional more agents. For treating or preventing asthma or chronic obstructive pulmonary disease, the compounds of Formula I may be combined with one or more agents selected from the group consisting of: ϑ-agonists (e.g., salmeterol), theophylline, anticholinergics (e.g., atropine and ipratropium bromide), cromolyn, nedocromil and leukotriene modifiers (e.g., montelukast). For treating or preventing inflammation, the compounds of Formula I may be combined with one or the following: a salicylate, including acetylsalicylic acid, a non-steroidal antiinflammatory drug, including indomethacin, sulindac, mefenamic, meclofenamic, tolfenamic, tolmetin, ketorolac, dicofenac, ibuprofen, naproxen, fenoprofen, ketoprofen, flurbiprofin and oxaprozin, a TNF inhibitor, including etanercept and infliximab, an IL-1 receptor antagonist, including anakinra, a cytotoxic or immunosuppressive drug, including methotrexate, leflunomide, azathioprine and cyclosporine, a gold compound, hydroxychloroquine or sulfasalazine, penicillamine, darbufelone, and a p38 kinase inhibitor. The compound of Formula I may also be used in combination with bisphonates such as alendronate to treat a glucocorticoid mediated disease and simultaneously inhibit osteoclast-mediated bone resorption.

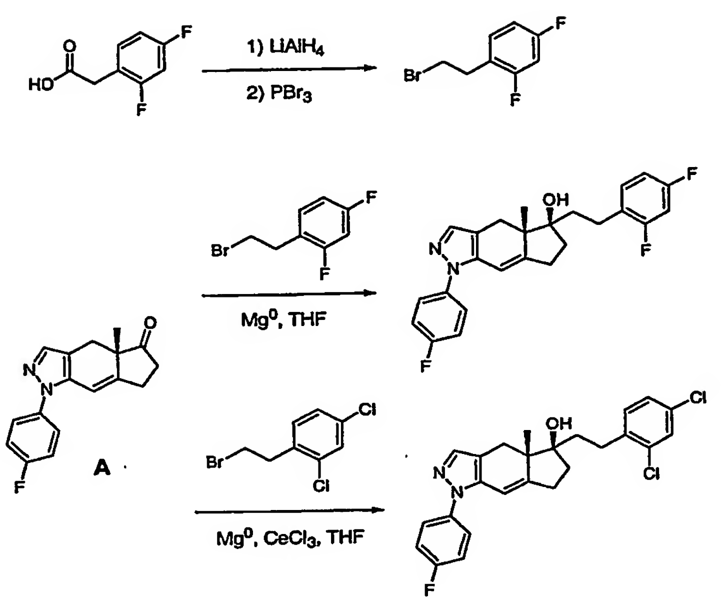
METHODS OF SYNTHESIS

The compounds of the invention are prepared by the following reaction schemes. All substituents are as defined above unless indicated otherwise.

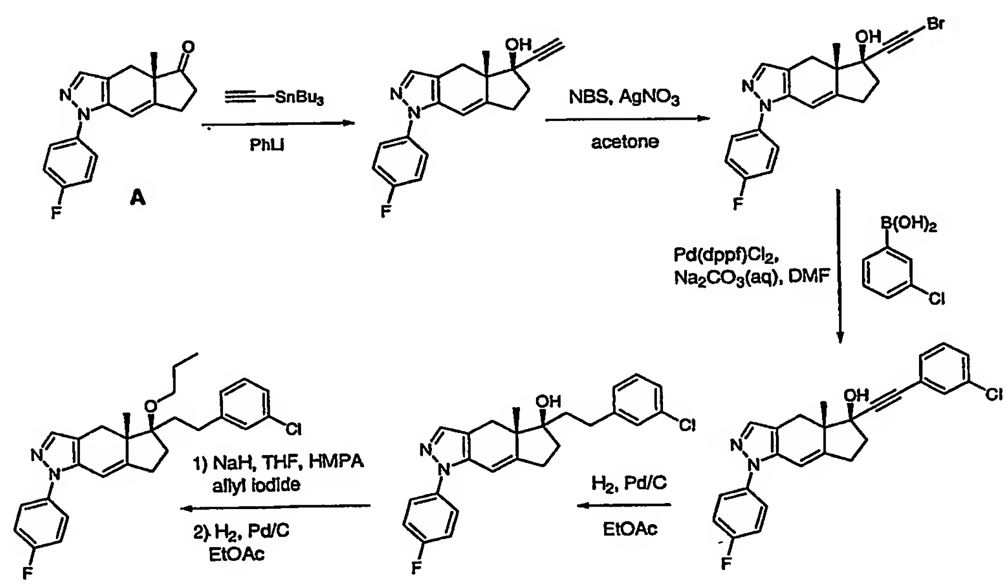
Scheme 1



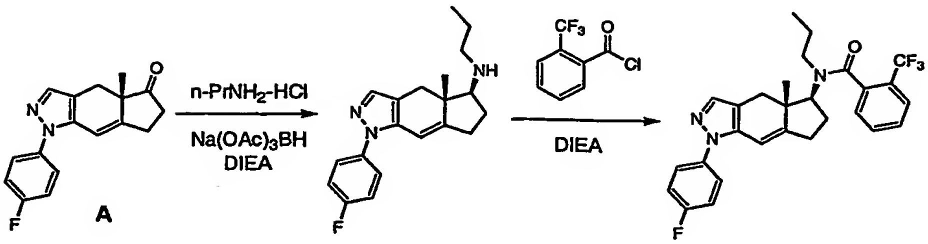
Scheme 2



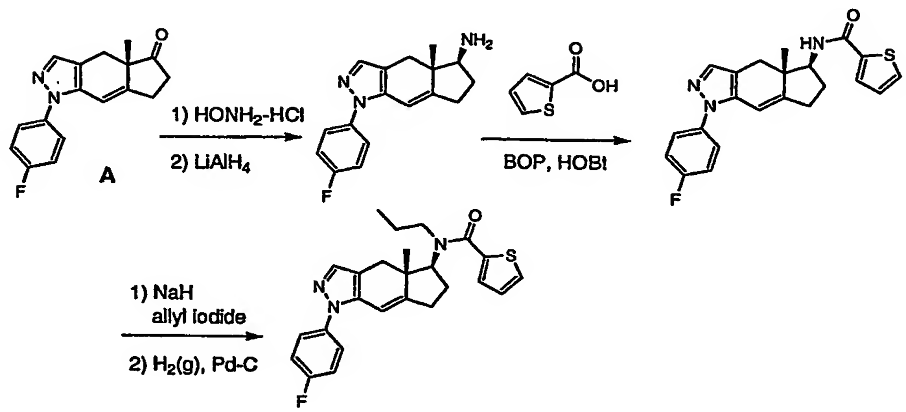
Scheme 3



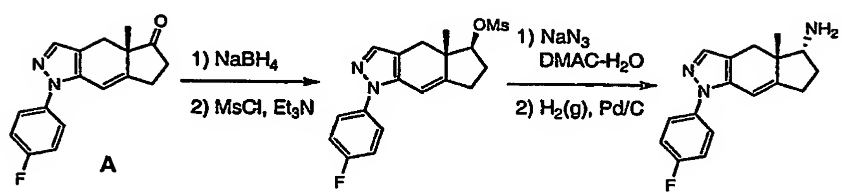
Scheme 4



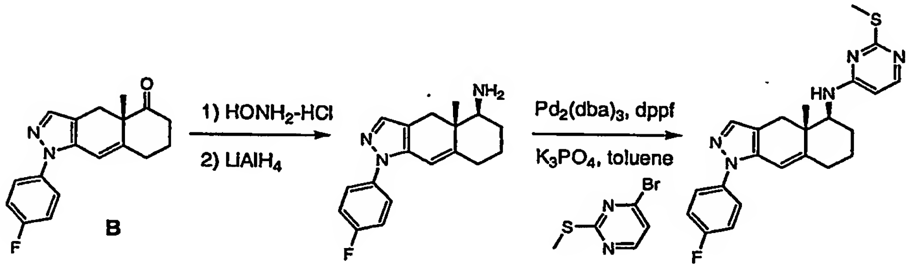
Scheme 5



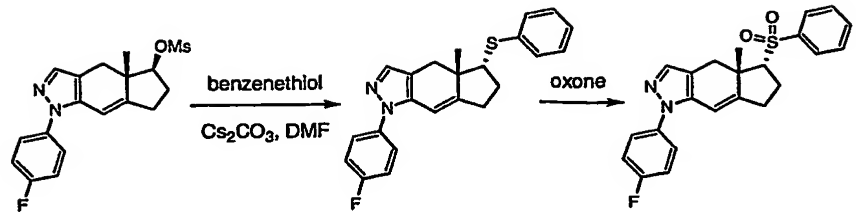
Scheme 6



Scheme 7



Scheme 8



REPRESENTATIVE EXAMPLES

The invention will now be illustrated by the following non-limiting examples in which, unless stated otherwise:

(i) all operations were carried out at room or ambient temperature, that is, at a temperature in the range 18-25°C;

(ii) evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 pascals: 4.5-30 mm. Hg) with a bath temperature of up to 60°C;

(iii) the course of reactions was followed by TLC and/or LCMS and reaction times are given for illustration only;

(iv) the structure and purity of all final products were assured by at least one of the following techniques: TLC, HPLC, MS or NMR spectrometry;

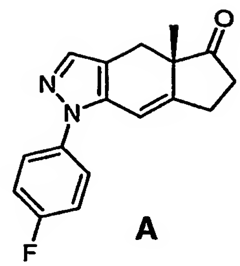
(v) yields, when given, are for illustration only;

(vi) when line-listed, NMR data is in the form of delta (δ) values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as internal standard, determined at 500 MHz or 600 MHz using the indicated solvent; conventional abbreviations used for signal shape are: s. singlet; d. doublet; t. triplet; m. multiplet; br. broad; etc.: in addition "Ar" signifies an aromatic signal;

(vii) chemical symbols have their usual meanings; the following abbreviations have also been used v (volume), w (weight), b.p. (boiling point), m.p. (melting point), L (litre(s)), mL (millilitres), g (gram(s)), mg (milligrams(s)), mol (moles), mmol (millimoles), eq or equiv (equivalent(s)), IC50 (molar concentration which results in 50% of maximum possible inhibition), uM (micromolar), nM (nanomolar).

PREPARATIVE EXAMPLES

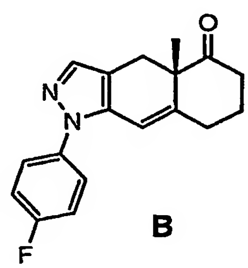
COMPOUND A



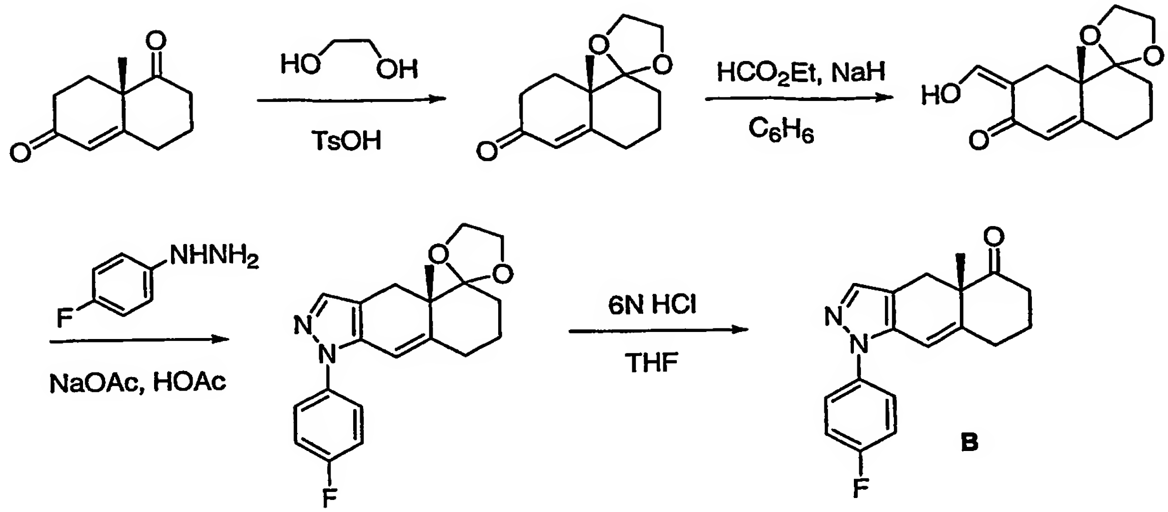
A

COMPOUND A was prepared from the known Hajos-Parrish ketone (*J. Org. Chem.* **1974**, *39(12)*, 1612-1621.) following the same reaction sequence and procedure described below for the preparation of **COMPOUND B**.

COMPOUND B



B



B

Step 1:

4 Å molecular sieves (~5 g) and *p*-toluenesulfonic acid (5.34g, 28.05 mmol) were added to a solution of the known Wieland-Miescher ketone (5 g, 28.05 mmol) (*Org. Synth.* **1961**, *41*, 38; CV-5, 486.) in ethylene glycol (140 mL). After stirring at room temperature for 23 min., the reaction was poured slowly into a 2:1 mixture of ice water/sat. aqueous $NaHCO_3$ (150 mL). The reaction was extracted with EtOAc (4 x 100 mL) and the combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (0 to 40% EtOAc/hexanes) on silica gel to afford 5.77g (93%) of the ketal as a white solid. LCMS = 223; $(M + 1)^+$. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.83 (br d, J = 1.8 Hz, 1H), 4.43-3.94 (m, 4H), 2.49-2.40 (m, 3H), 2.39-2.27 (m, 2H), 1.95-1.88 (m, 1H), 1.84-1.78 (m, 1H), 1.76-1.64 (m, 3H), 1.37 (s, 3H).

Step 2:

Ethyl formate (7.36 mL, 86.48 mmol) and sodium hydride (60% suspension in mineral oil; 3.46 g, 86.48 mmol) were added to a cooled solution (–40 °C) of the ketal in anhydrous benzene (200 mL). MeOH (450 TL) was added dropwise over 15 min. and the reaction allowed to warm to room temperature. After stirring for 3 h, the reaction was cooled to 0 °C and 50 mL H_2O was added. The biphasic system was shaken and the organic layer was washed with H_2O (3 x 50 mL). The combined aqueous layers were washed with diethyl ether (100 mL) and then acidified to pH 5.5-6 with sat. aqueous KH_2PO_4. The aqueous layer was extracted with EtOAc (5 x 200 mL). The combined extracts were dried over Na_2SO_4 and concentrated *in vacuo* to afford 5.04 g (93%) of hydroxyketone product as an orange oil. LCMS = 251; $(M + 1)^+$.

Step 3:

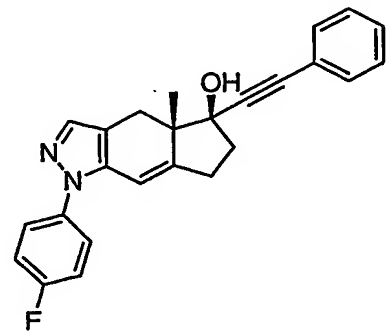
The hydroxyketone (4.1 g, 16.4 mmol) was dissolved in glacial acetic acid (40mL) and *para*-fluorophenylhydrazine hydrocloride (2.8 g, 17.22 mmol) and sodium acetate (1.41 g, 17.22 mmol) were added. After stirring at room temperature for 2 h, the reaction was poured slowly into 10% $NaHCO_3$ (1 L) and extracted with EtOAc (6 x 500 mL). The combined extracts were washed with brine (500 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by flash chromatography (10% EtOAc/hexanes) on silica gel to afford 2.26 g (41%) of the pyrazole ketal as an orange solid. LCMS = 421; $(M + 1)^+$. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.47-7.44 (m, 2H), 7.43 (s, 1H), 7.18-7.16 (d, *J* = 8.5 Hz, 1H), 7.16-7.14 (d, *J* = 8.7 Hz, 1H), 6.22 (br d, *J* = 2.2 Hz, 1H), 4.11-4.01 (m, 4H), 3.20-3.16 (d, *J* = 15.7 Hz, 1H), 2.54-2.51 (d, *J* = 16 Hz, 1H), 2.51-2.40 (m, 1H), 2.34-2.28 (m, 1H), 1.88-1.64 (m, 4H), 1.23 (s, 3H).

Step 4:

The pyrazole ketal (2.26 g; 6.65 mmol) was dissolved in THF (65 mL) and 6N HCl (4.43 mL, 26.6 mL) was added. The reaction was heated at 65 °C for 3.5 h and then poured slowly into 10% $NaHCO_3$ (150 mL). The mixture was extracted with EtOAc (4 x 250 mL) and the combined extracts washed with brine (2 x 200 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford 1.97 g (100%) of **COMPOUND B** as a brown oil. LCMS = 297; $(M + 1)^+$. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.50 (s, 1H), 7.49-7.45 (m, 2H), 7.20-7.16 (m, 2H), 6.31 (br d, *J* = 2 Hz, 1 H), 2.96-2.88 (m, 2H), 2.72-2.62 (m, 2H), 2.59-2.53 (m, 2H), 2.14-2.80 (m, 1H), 1.75-1,64 (qt, *J* = 13.1 Hz, J = 4.3 Hz, 1H), 1.27 (s, 3H).

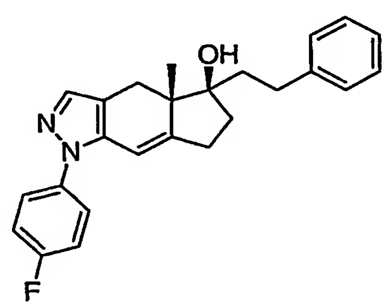
EXAMPLES

EXAMPLE 1



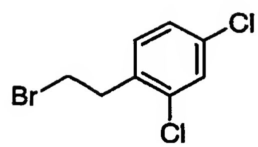
COMPOUND A (1.0 g, 3.53 mmol) was dissolved in 10 mL of anhydrous THF under argon atmosphere and cooled to –50 °C. Then 4.0 equiv of phenylethynyl magnesium bromide (1M in THF, 14.12 mmol, 14 mL) was added dropwise. The resulting reaction mixture was then allowed to slowly warm to 23 °C over 6 h. The reaction was quenched with 100 mL of saturated aqueous NH_4Cl, extracted with methylene chloride (3 x 75 mL) and the result organic layers were dried over sodium sulfate and evaporated under reduced pressure. The crude reaction mixture was purified by flash column chromatography (SiO_2, EtOAc/hexanes) to give the desired product as a yellow foam. The product was characterized by ^{1}H NMR, HPLC and mass spectroscopy (m/z: 385 (M^++1)).

EXAMPLE 2



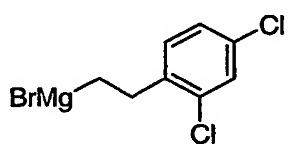
EXAMPLE 1 (408 mg, 1.41 mmol) was dissolved in 10 mL EtOAc and 10% Pd/C (100mg) was added. The reaction mixture was stirred under hydrogen atmosphere (1 atm) for 20 min before it was filtered through celite, washed with EtOAc (50 mL) and evaporated under reduced pressure. The crude reaction mixture was purified by flash column chromatography (SiO_2, acetone/hexanes) to give the desired product as a pale yellow foam. The product was characterized by ^{1}H NMR, HPLC and mass spectroscopy (m/z: 389 (M^++1)).

COMPOUND I



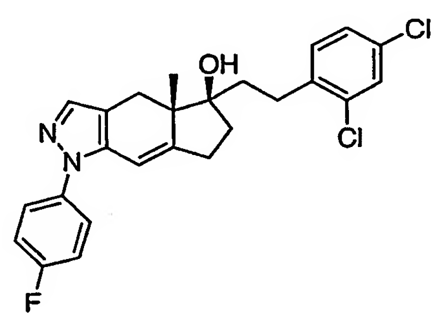
2,4-Dichlorophenethyl alcohol (10 g, 52.0 mmol) was dissolved in 100 mL of methylene chloride, cooled to 0 °C under nitrogen atmosphere and 1.5 equiv of phosphorous tribromide (1M in CH_2Cl_2, 80 mmol, 80 mL) was added dropwise. The resulting reaction mixture was warmed to 23 °C and stirred for 2 h before the very slow addition of 200 mL of saturated aqueous sodium bicarbonate and extraction with methylene chloride (2 x 150 mL). The combined organic layers were dried over sodium sulfate and evaporated under reduced pressure. The crude product was purified by a SiO_2 plug (5% EtOAc/hexanes) to yield 2,4-dichlorophenethyl bromide. The product was characterized by ^{1}H NMR and HPLC.

COMPOUND II



COMPOUND I (254 mg, 1.0 mmol) was dissolved in 2 mL THF under an argon atmosphere and 1.0 equiv of magnesium turnings (24 mg, 1 mmol) was added. The resulting suspension was briefly heated then allowed to stir until all the magnesium had reacted (2 h). This 0.5M solution of 2,4-dichlorophenethyl magnesium bromide was used in the following transformation to generate **EXAMPLE 3.**

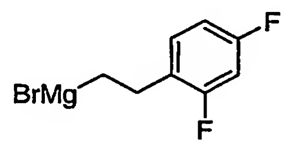
EXAMPLE 3



COMPOUND A (100 mg, 0.336 mmol) was dissolved in 2 mL of anhydrous THF under an argon atmosphere and 3.0 equiv anhydrous $CeCl_3$ (1.0 mmol, 246 mg) was added and the

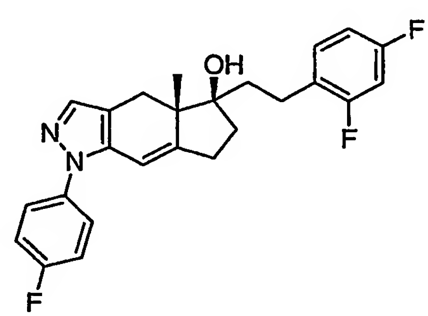
resulting suspension was placed in a sonicator at 23 °C for 30 min followed by additional stirring (1 h). This reaction mixture was then cooled to –30 °C and 3.0 equiv of a solution of **COMPOUND II** (0.5 M in THF, 1.0 mmol, 2 mL) was added. The resulting reaction mixture was allowed to slowly warm to 23 °C over 15 h. The reaction was quenched with 35 mL of 1N HCl, extracted with methylene chloride (3 x 20mL) and the result organic layers were dried over sodium sulfate and evaporated under reduced pressure. The crude reaction mixture was purified by flash column chromatography (SiO_2, EtOAc/hexanes) to give the desired product as a yellow foam. The product was characterized by ^1H NMR, HPLC and mass spectroscopy (m/z: 457 (M^++1)).

COMPOUND III



Lithium aluminum hydride (65 g) was suspended in dry THF (1.5 L) under a nitrogen atmosphere and this mixture was then treated with a solution of 2,4-difluorophenylacetic acid (169 g) in dry THF (1 L) over a period of 90 min at 0 °C. The reaction mixture was stirred for 70 min at 0 °C and then quenched dropwise with the slow addition of 20% w/v $KOH_{(aq)}$ (340 mL) at 0 °C. The inorganic salts were then filtered over Hi flo (200 g) and $MgSO_4$ (200 g), washed with ethyl acetate (200 g), and the filtrate concentrated in vacuo to provide the 2,4-difluorophenethyl alcohol. This alcohol was brominated and converted to its Grignard salt in the same manner described for **COMPOUNDS I** and **II** respectively. This 0.5M solution of 2,4-difluorophenethyl magnesium bromide was used in the following transformation to generate **EXAMPLE 4.**

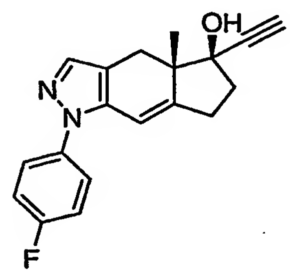
EXAMPLE 4



COMPOUND A (200 mg, 0.71 mmol) was dissolved in 4 mL of anhydrous THF under argon atmosphere, cooled to –30 °C, and 5.0 equiv of a solution of **COMPOUND III** (0.5M in THF,

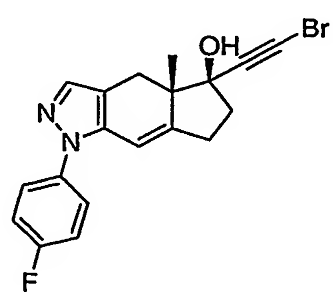
3.54 mmol, 7 mL) was added. The resulting reaction mixture was allowed to slowly warm to 23 °C over 15 h. The reaction was quenched with 50 mL of saturated aqueous NH_4Cl, extracted with methylene chloride (3 x 30 mL) and the result organic layers were dried over sodium sulfate and evaporated under reduced pressure. The crude reaction mixture was purified by flash column chromatography (SiO_2, Et_2O/hexanes) to give the desired product as a tan foam. The product was characterized by ^1H NMR, HPLC and mass spectroscopy (m/z: 425 (M^++1)).

EXAMPLE 5



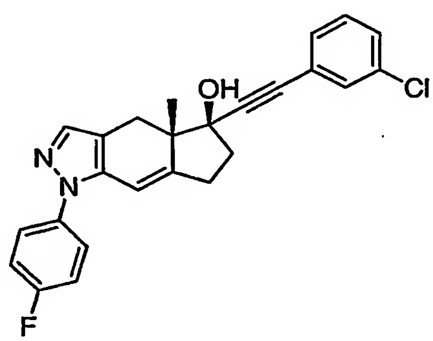
Tributylethynyl tin (6.73 mmol, 16 mL) was dissolved in 40 mL anhydrous THF under an argon atmosphere and cooled to –80 °C. Phenyl lithium (1.8M in THF, 56.73 mmol, 32 mL) was added, and the resulting reaction mixture was allowed to stir for 5 min. Then **COMPOUND A** (4.0 g, 14.18 mmol) in 40 mL anhydrous THF was added dropwise, and the reaction mixture was warmed to 23 °C over 3 h. The reaction was then quenched with 300 mL of saturated aqueous NH_4Cl, extracted with methylene chloride (3 x 100 mL) and the resulting combined organic layers were dried over sodium sulfate and evaporated under reduced pressure. The crude reaction mixture was purified by flash column chromatography (SiO_2, EtOAc/hexanes) to give the desired destannylated product as a white foam along with a trace of the tributylstannane product and a minor amount of recovered starting material. The product was characterized by ^1H NMR, HPLC and mass spectroscopy (m/z: 309 (M^++1)).

EXAMPLE 6



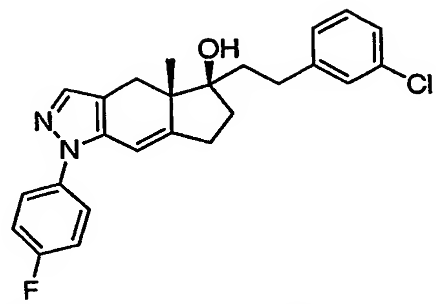
EXAMPLE 5 (4.0 g, 13.05 mmol) was dissolved in acetone and *N*-bromosuccinimide (15.58 mmol, 2.8 g) and catalytic $AgNO_3$ (50 mg) were added. After 2.5 h, additional *N*-bromosuccinimide (250 mg) was added. After 1 h the reaction was complete and the reaction mixture was diluted with 300 mL H_2O, extracted with EtOAc (3 x 100 mL) and the resulting combined organic layers were dried over sodium sulfate and evaporated under reduced pressure. The crude reaction mixture was purified by flash column chromatography (SiO_2, acetone/hexanes) to give the desired product as a white solid. The product was characterized by ^{1}H NMR, HPLC and mass spectroscopy (m/z: 389 (M^++1)).

EXAMPLE 7



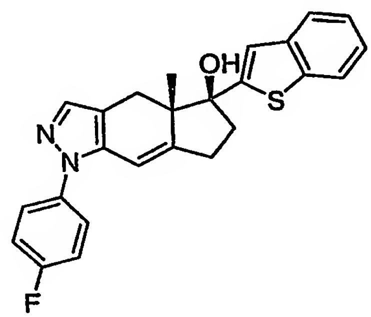
EXAMPLE 6 (4.76 g, 12.33 mmol) was dissolved in 80 mL of degassed DMF under argon atmosphere and 3.0 equiv of aqueous degassed Na_2CO_3 (2M, 37.0 mmol, 18 mL), 1.5 equiv of 3-chlorophenyl boronic acid (18.49 mmol, 3.0 g), and dichloro [1,1'-bis(diphenylphosphino)ferrocene] palladium (II) dichloromethane adduct (500 mg) were added. The resulting suspension was heated to 90 °C for 2 h, then quenched by the addition of 400 mL of H_2O. The mixture was then extracted with dichloromethane (3 x 200 mL) and the resulting combined organic layers were dried over sodium sulfate and evaporated under reduced pressure. The crude reaction mixture was purified by flash column chromatography (SiO_2, EtOAc/hexanes) to give the desired product as a light orange oil. The product was characterized by ^{1}H NMR, HPLC and mass spectroscopy (m/z: 419 (M^++1)).

EXAMPLE 8



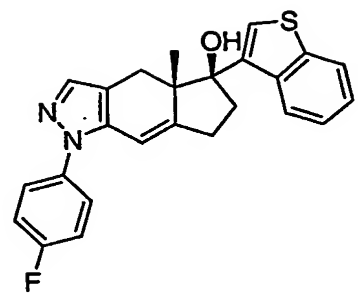
EXAMPLE 7 (3.7 g, 8.88 mmol) was dissolved in 80 mL EtOAc and 10% Pd/C (600mg) was added. The reaction mixture was stirred under hydrogen atmosphere (2 atm) for 6 h before it was filtered through celite, washed with EtOAc (250 mL) and evaporated under reduced pressure. The crude reaction mixture was purified by flash column chromatography (SiO_2, acetone/hexanes) to give the desired product as a pale yellow foam. The product was characterized by ^1H NMR, HPLC and mass spectroscopy (m/z: 423 (M^++1)).

EXAMPLE 9



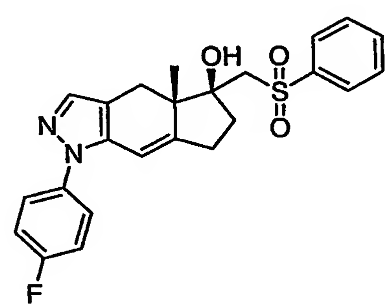
Benzothiophene (3.0 equiv) was dissolved in 2 mL of anhydrous THF under argon atmosphere and cooled to –80 °C. Then 3.0 equiv of *n*-butyl lithium (1.6 M in THF, 0.504 mmol, 0.32 mL) was added. After 15 min, **COMPOUND A** (50 mg, 0.168 mmol) in 1.0 mL THF was added dropwise and the resulting reaction mixture was then allowed to slowly warm to 23 °C over 6 h. The reaction mixture was quenched with 20 mL of saturated aqueous NH_4Cl, extracted with methylene chloride (3 x 15 mL) and the organic phase was dried over sodium sulfate and evaporated under reduced pressure. The crude reaction mixture was purified by flash column chromatography (SiO_2, EtOAc/hexanes) to give the desired product as a yellow foam. The product was characterized by ^1H NMR, HPLC and mass spectroscopy (m/z: 417 (M^++1)).

EXAMPLE 10



3-Bromobenzothiophene (2.0 equiv) of was dissolved in 2 mL of anhydrous THF under argon atmosphere and cooled to –80 °C and 4.0 equiv of *tert*-butyl lithium (1.5 M in THF, 0.672 mmol, 0.45 mL) was added. After 5 min, **COMPOUND A** (50 mg, 0.168 mmol) in 1.0 mL THF was added dropwise and the resulting reaction mixture was slowly warmed to 23 °C over 6 h. The reaction mixture was quenched with 20 mL of saturated aqueous NH_4Cl, extracted with methylene chloride (3 x 15 mL) and the organic phase was dried over sodium sulfate and evaporated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, EtOAc/hexanes) to give the desired product as a yellow foam. The product was characterized by ^{1}H NMR, HPLC and mass spectroscopy (m/z: 417 (M^++1)).

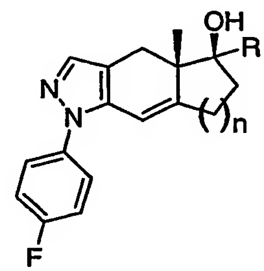
EXAMPLE 11



Methyl phenyl sulfone (3 equiv) was dissolved in 1.5 mL of anhydrous THF under an argon atmosphere and cooled to –10 °C, and 4.0 equiv of n-butyl lithium (1.5 M in THF, 0.672 mmol, 0.45 mL) was added. After 1 h at 0 °C, **COMPOUND A** (50 mg, 0.168 mmol) in 1.0 mL THF was added dropwise and the resulting reaction mixture was then allowed to slowly warm to 23 °C over 3 h. The reaction mixture was quenched with 20 mL of saturated aqueous NH_4Cl, extracted with methylene chloride (3 x 15 mL) and the organic phase was dried over sodium sulfate and evaporated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, EtOAc/hexanes) to give the desired product as a yellow foam. The product was characterized by ^{1}H NMR, HPLC and mass spectroscopy (m/z: 439 (M^++1)).

EXAMPLES 12-87

The following compounds were prepared under conditions similar to those described in the examples above and illustrated in Schemes 1-3. Where R=H, a sodium borohydride reduction of **COMPOUNDS A** and **B** was conducted as described in **EXAMPLE 210** below. The following examples were characterized by ^{1}H NMR, HPLC and mass spectrometry.



EX.	**n**	**R Group**	**MS (m/z) (M^+ +1)**
12	1	vinyl	311
13	2	vinyl	325
14	1	allyl	325
15	2	allyl	339
16	1	3-butenyl	339
17	2	3-butenyl	353
18	2	*n*-butyl	355
19	1	*n*-pentyl	355
20	2	*n*-pentyl	369
21	2	*n*-hexyl	383

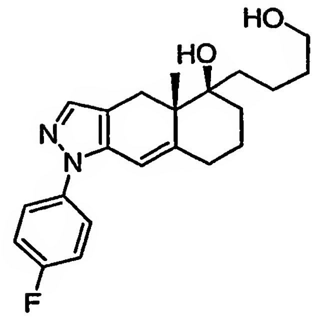
22	1	3-methylbutyl	355
23	2	3-methylbutyl	369
24	1	2-cyclohexylethyl	395
25	2	2-cyclohexylethyl	409
26	1	3,3-dimethylbutyl	369
27	2	3,3-dimethylbutyl	383
28	1	4-methyl-3-pentenyl	367
29	2	4-methyl-3-pentenyl	381
30	1	4,4,4-trifluorobutyl	395
31	2	4,4,4-trifluorobutyl	409
32	1	3,4,4-trifluoro-3-butenyl	393
33	2	3,4,4-trifluoro-3-butenyl	407
34	1	3-methoxypropyl	357
35	2	3-methoxypropyl	371
36	2	benzyl	389
37	2	phenyl	375
38	2	phenethyl	403

39	2	3-phenylpropyl	417
40	1	2-(2-chlorophenyl)ethyl	423
41	2	2-(2-chlorophenyl)ethyl	437
42	2	2-(3-chlorophenyl)ethyl	437
43	1	2-(4-chlorophenyl)ethyl	423
44	2	2-(4-chlorophenyl)ethyl	437
45	2	2-(2,4-dichlorophenyl)ethyl	471
46	1	2-(4-fluorophenyl)ethyl	407
47	2	2-(4-fluorophenyl)ethyl	421
48	1	2-(2,5-difluorophenyl)ethyl	425
49	1	2-(2,3-difluorophenyl)ethyl	425
50	1	2-(3,5-difluorophenyl)ethyl	425
51	1	2-(4-methoxyphenyl)ethyl	419
52	2	2-(4-methoxyphenyl)ethyl	433
53	1	2-(2-naphthyl)ethyl	439
54	2	2-(2-naphthyl)ethyl	453
55	2	2-(2,4-difluorophenyl)ethyl	439

56	1	2-(3-(trifluoromethyl)phenyl)ethyl	457
57	2	2-(3-(trifluoromethyl)phenyl)ethyl	471
58	1	2-(2-methoxyphenyl)ethyl	419
59	2	2-(2-methoxyphenyl)ethyl	433
60	1	2-(4-*tert*-butylphenyl)ethyl	445
61	2	2-(4-*tert*-butylphenyl)ethyl	459
62	1	2-(4-methylphenyl)ethyl	403
63	2	2-(4-methylphenyl)ethyl	417
64	1	2-(1-naphthyl)ethyl	439
65	2	2-(1-naphthyl)ethyl	453
66	1	2-(2-methylphenyl)ethyl	403
67	2	2-(2-methylphenyl)ethyl	417
68	1	2-(3-methylphenyl)ethyl	403
69	2	2-(3-methylphenyl)ethyl	417
70	1	2-(2-fluorophenyl)ethyl	407
71	1	2-(3-fluorophenyl)ethyl	407
72	1	2-(3,4-dichlorophenyl)ethyl	458

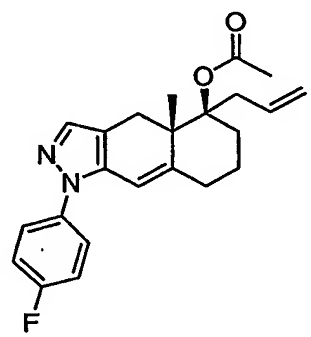
73	1	2-(2-chloro-4-fluorophenyl)ethyl	441
74	1	2-(3-thiopheneyl)ethyl	395
75	1	3-(*N*-pyrrolyl)propyl	392
76	2	3-(*N*-pyrrolyl)propyl	406
77	1	*E*-2-phenylethenyl	387
78	2	*E*-2-phenylethenyl	401
79	1	*Z*-2-phenylethenyl	387
80	2	*Z*-2-phenylethenyl	401
81	2	2-phenylethynyl	399
82	1	2-(2,4-difluorophenyl)ethynyl	421
83	1	2-(2-thiopheneyl)ethyl	395
84	1	2-(3,4-difluorophenyl)ethyl	425
85	1	2-(3,4,5-trifluorophenyl)ethyl	443
86	2	H	299
87	1	H	285

EXAMPLE 88



EXAMPLE 17 (14 mg, 0.039 mmol) was dissolved in 1.0 mL THF under argon atmosphere and cooled to 0 °C and 4.0 equiv of 9-BBN (0.5M in THF, 0.156 mmol, 0.312 mL) were added. The reaction mixture was allowed to warm to 23 °C and stir for 15 h before being quenched by the addition of 1 mL of ethanol, 0.052 mL of 6N aqueous NaOH, and 0.1 mL of 30% aqueous hydrogen peroxide. The reaction was then diluted with 5.0 mL of water , extracted with methylene chloride (3 x 4 mL) and the organic phase was dried over sodium sulfate and evaporated under reduced pressure. The crude residue was purified by preparative thin layer chromatography (SiO_2, EtOAc/hexanes) to give the desired product as a clear film. The product was characterized by ^1H NMR, HPLC and mass spectroscopy (m/z: 371 (M^++1)).

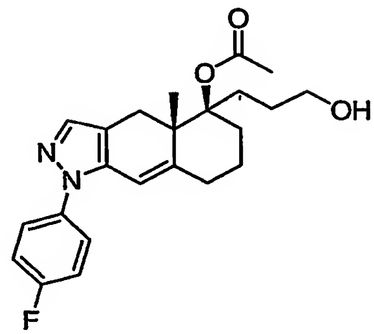
EXAMPLE 89



EXAMPLE 15 (60 mg, 0.178 mmol) was dissolved in 2.0 mL THF under argon atmosphere and cooled to -10 °C and 2.0 equiv of methyl magnesium bromide (1.0M in THF, 0.356 mmol, 0.35 mL) was added. After 5 min, acetic anhydride (0.267 mmol, 0.25 mL) was added and the resulting reaction mixture was warmed to 65 °C for 15 h. The reaction was then quenched with 10 mL of saturated aqueous NH_4Cl, extracted with methylene chloride (3 x 10 mL) and the organic phase was dried over sodium sulfate and evaporated under reduced pressure. The crude reaction mixture was purified by flash column chromatography (SiO_2, EtOAc/hexanes) to give

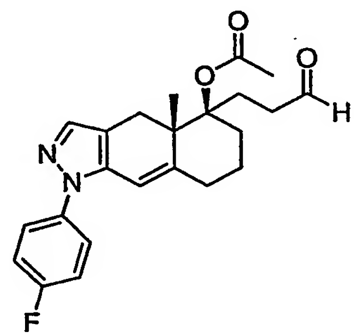
the desired product as a white foam. The product was characterized by ^{1}H NMR, HPLC and mass spectroscopy (m/z: 381 (M^++1)).

EXAMPLE 90



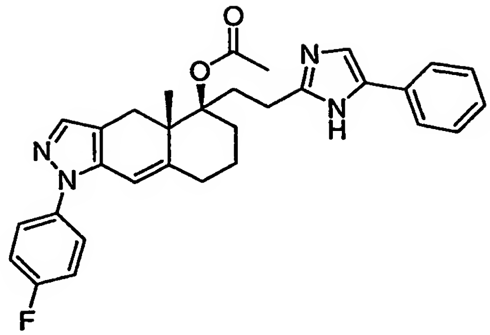
EXAMPLE 90 was prepared from **EXAMPLE 89** according to the above procedure described in **EXAMPLE 88**. The product was characterized by ^{1}H NMR, HPLC and mass spectroscopy (m/z: 399 (M^++1)).

EXAMPLE 91



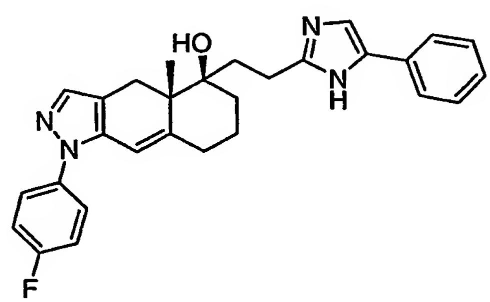
EXAMPLE 90 (25 mg, 0.059 mmol) was dissolved in 2.0 mL methylene chloride under an argon atmosphere and cooled to 0 °C. Then 20 equiv of pyridine (1.18 mmol, 0.094 mL) and 3.0 equiv of Dess-Martin periodinane (0.177 mmol, 75 mg) were added, and the resulting reaction mixture was slowly warmed to 23 °C over 3 h. The reaction was quenched with 20 mL of saturated aqueous NH_4Cl, extracted with methylene chloride (3 x 15 mL) and the organic phase was dried over sodium sulfate and evaporated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, EtOAc/hexanes) to give the desired product as a yellow oil. The product was characterized by ^{1}H NMR, HPLC and mass spectroscopy (m/z: 397 (M^++1)).

EXAMPLE 92



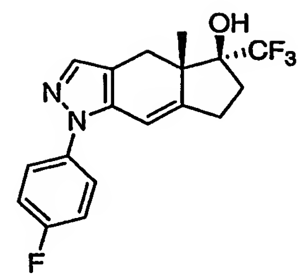
EXAMPLE 91 (15 mg, 0.038 mmol) was dissolved in 1.0 mL MeOH under an argon atmosphere, and 10 equiv of ammonium acetate (0.38 mmol, 30 mg) and 3.0 equiv of phenyl glyoxal (0.114 mmol, 16 mg) were added. The resulting reaction mixture was heated at 65 °C for 15 h, cooled and evaporated under reduced pressure. The crude residue was then purified by flash column chromatography (SiO_2, ethyl ether/hexanes) to give the desired product as a yellow foam. The product was characterized by ^{1}H NMR, HPLC and mass spectroscopy (m/z: 511 (M^++1)).

EXAMPLE 93



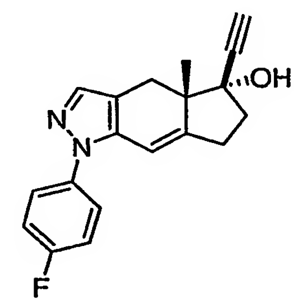
EXAMPLE 92 (7 mg, 0.014 mmol) was dissolved in 0.5 mL anhydrous MeOH and cooled to 0 °C and 2.0 equiv of potassium carbonate (0.027 mmol, 4.0 mg) was added. After 2 h the reaction mixture was diluted with 10 mL of water, extracted with methylene chloride (3 x 10 mL) and the organic phase was dried over sodium sulfate and evaporated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, EtOAc/hexanes) to give the desired product as a yellow film. The product was characterized by ^{1}H NMR, HPLC and mass spectroscopy (m/z: 469 (M^++1)).

EXAMPLE 94



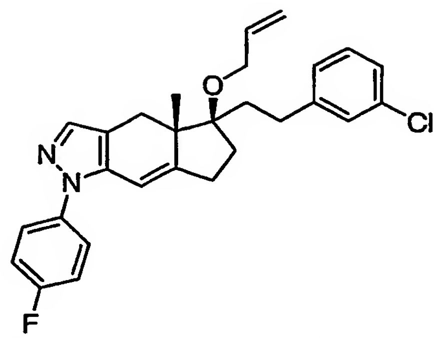
COMPOUND A (50 mg, 0.168 mmol) was dissolved in 1.0 mL THF under an argon atmosphere and $(CF_3)Si(CH_3)_3$ [0.5 M in THF] (0.504 mmol, 1.0 mL) followed by catalytic tetrabutylammonium fluoroide [1 M in THF] (0.005 mL) were added. The resulting reaction mixture was allowed to stir for 15 hours before being diluted with 25 mL of aqueous 1N HCl, extracted with methylene chloride (3 x 20 mL), and the organic phase was dried over anhydrous sodium sulfate and evaporated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, EtOAc/hexanes) to give the desired product as a yellow oil. The product was characterized by ^{1}H NMR, HPLC and mass spectroscopy (m/z: 353 (M^++1)).

EXAMPLE 95



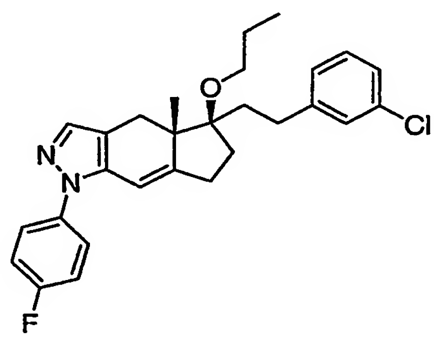
EXAMPLE 5 was acetylated under conditions described for **EXAMPLE 89**. This propargylic acetate (20 mg, 0.168 mmol) was dissolved in 0.5 mL THF under an argon atmosphere and benzylamine (0.11 mmol, 0.12 mL) followed by catalytic copper (I) chloride (3 mg) were added. The resulting reaction mixture was heated at 100 °C in a sealed tube for 2 hours before it was cooled to room temperature, diluted with 20 mL of H_2O, extracted with methylene chloride (3 x 20 mL), and the organic phase was dried over anhydrous sodium sulfate and evaporated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, EtOAc/hexanes) to give the desired product as a clear oil. The product was characterized by ^{1}H NMR, HPLC and mass spectroscopy (m/z: 309 (M^++1)).

EXAMPLE 96



EXAMPLE 8 (3.0 g, 7.10 mmol) was dissolved in 40 mL of 5:1 THF/HMPA under argon atmosphere and sodium hydride (60% in mineral oil, 28.44 mmol, 1.0 g) was added and the reaction mixture was allowed to stir for 10 min at 23 °C. Allyl iodide (35.54 mmol, 3.2 mL) was then added and the reaction was heated to 100 °C for 3 h before cooling to 23 °C. The reaction was then quenched by the addition of 250 mL of saturated aqueous NH_4Cl, extracted with methylene chloride (3 x 100 mL) and the result organic layers were dried over sodium sulfate and evaporated under reduced pressure. The crude reaction mixture was purified by flash column chromatography (SiO_2, acetone/hexanes) to give the desired product as an orange foam. The product was characterized by ^1H NMR, HPLC and mass spectroscopy (m/z: 463 (M^++1)).

EXAMPLE 97

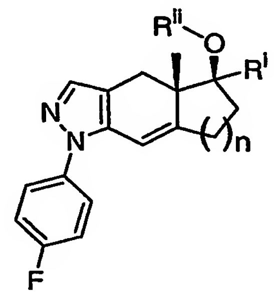


EXAMPLE 96 (2.32 g, 5.02 mmol) was dissolved in 30 mL EtOAc and 10% Pd/C (300mg) was added. The reaction mixture was stirred under a hydrogen atmosphere (1 atm) for 2 h before it was filtered through celite, washed with EtOAc (200 mL) and evaporated under reduced pressure. The crude reaction mixture was purified by flash column chromatography (SiO_2, acetone/hexanes) to give the desired product as a white foam. The product was characterized by ^1H NMR, HPLC and mass spectroscopy (m/z: 465 (M^++1)).

EXAMPLES 98-125

The following compounds were prepared under conditions similar to those described in the examples above and illustrated in Scheme 3. Other alkyl halides known to those skilled in the

art were used in place of allyl iodide to generate the ethers shown in the table below. As described in **EXAMPLE 97**, hydrogenation was also used to generate some of the saturated ethers shown in the table below. The following examples were characterized by ^{1}H NMR, HPLC and mass spectrometry.

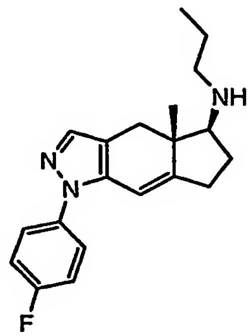


EX.	n	R^{i} Group	R^{ii} Group	MS (m/z) (M^{+}+1)
98	1	H	*n*-propyl	327
99	2	allyl	allyl	379
100	1	phenethyl	cyclopropylmethyl	443
101	1	phenethyl	*E*-2-butenyl	443
102	1	2-(2,4-dichlorophenyl)ethyl	methyl	471
103	1	2-(2-chlorophenyl)ethyl	methyl	437
104	1	2-(3-chlorophenyl)ethyl	methyl	437
105	1	*n*-pentyl	methyl	369
106	1	2-(4-fluorophenyl)ethyl	methyl	421
107	2	phenethyl	methyl	417

108	1	2-(2,4-dichlorophenyl)ethyl	benzyl	547
109	1	2-(2,4-dichlorophenyl)ethyl	allyl	497
110	1	2-(2,4-dichlorophenyl)ethyl	*n*-propyl	499
111	1	2-(2-chlorophenyl)ethyl	*n*-propyl	465
112	1	phenethyl	*n*-propyl	431
113	1	phenethyl	methyl	403
114	1	2-(3-chlorophenyl)ethynyl	allyl	459
115	1	2-(3-chlorophenyl)ethynyl	*n*-propyl	461
116	1	2-(2,4-difluorophenyl)ethyl	methyl	439
117	2	2-(2,4-difluorophenyl)ethyl	methyl	453
118	1	phenethyl	*E*-2-pentenyl	457
119	1	trifluoromethyl	allyl	393
120	1	trifluoromethyl	*n*-propyl	395
121	1	2-(3-methylphenyl)ethyl	methyl	417
122	1	phenethyl	*n*-butyl	445
123	1	phenethyl	*n*-pentyl	459
124	1	2-(3,4-difluorophenyl)ethyl	*n*-propyl	467

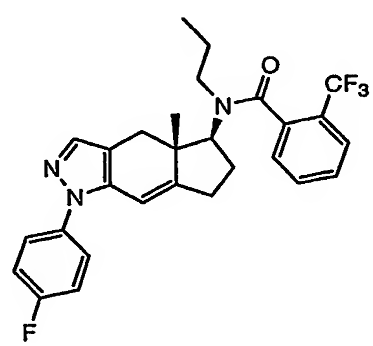
125	1	2-(3-fluorophenyl)ethyl	methyl	421

EXAMPLE 126



COMPOUND A (250 mg, 0.88 mmol) was diluted into CH_2Cl_2 (11 mL), and treated with *n*-propylamine hydrochloride (842 mg, 8.87 mmol), diisopropylethylamine (2.4 mL, 13.3 mmol), and followed by sodium triacetoxyborohydride (376 mg, 1.77 mmol). The reaction mixture was maintained at 23 °C for 15 h. The mixture was then partitioned between $NaHCO_{3(aq)}$ and CH_2Cl_2, and the organic phase was dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was either used directly in subsequent reactions or purified by flash chromatography (Biotage 40S, SiO_2, 1:9:90 NH_4OH-MeOH-$CHCl_3$) to provide the product which was characterized by ^1H NMR, HPLC and mass spectrometry (m/z: 326 (M^++1)).

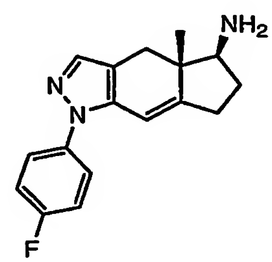
EXAMPLE 127



EXAMPLE 126 (2 g, 6.15 mmol) was diluted into CH_2Cl_2 (31 mL) and treated with diisopropylethylamine (2.3 mL, 12.3 mmol), followed by 2-(trifluoromethyl)benzoyl chloride (1.4 mL, 9.23 mmol). The reaction mixture was maintained at 23 °C for 2 h. The mixture was then partitioned between $NaHCO_{3(aq)}$ and CH_2Cl_2, the organic phase dried over anhydrous

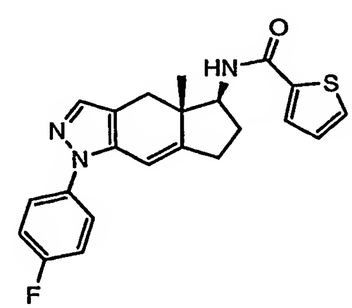
sodium sulfate, concentrated in vacuo and purified by flash chromatography (Biotage 65M, SiO_2, 30% EtOAc-hexane) to provide the product which was characterized by ^{1}H NMR, HPLC and mass spectrometry (m/z: 498 (M^++1)).

EXAMPLE 128



COMPOUND A (200 mg, 0.71 mmol) was diluted into pyridine (2 mL), treated with hydroxylamine hydrochloride (56 mg, 0.81 mmol), and the mixture heated at 90 °C for 2 h. The reaction mixture was then partitioned between 0.01N $HCl_{(aq)}$ and CH_2Cl_2, the organic phase dried over anhydrous sodium sulfate and concentrated in vacuo. The crude oxime intermediate was diluted into anhydrous THF (6 mL) and treated with solid lithium aluminum hydride (230 mg, 6.05 mmol). The reaction mixture was maintained at 23 °C for 16 h, partitioned between (1:1) Rochelle's salt / $NaHCO_{3(aq)}$ and $CHCl_3$, the organic phase dried over anhydrous sodium sulfate and concentrated in vacuo. The crude primary amine which was characterized by ^{1}H NMR, HPLC and mass spectrometry (m/z: 284 (M^++1)) was used directly in subsequent reactions.

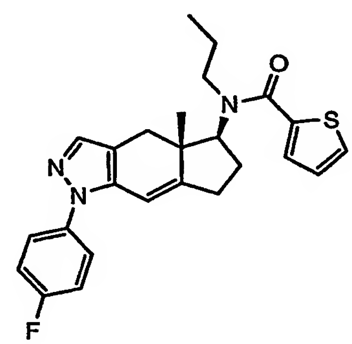
EXAMPLE 129



EXAMPLE 128 (6 mg, 0.021 mmol) was diluted into CH_2Cl_2 (0.5 mL), treated with 2-thiophenecarboxylic acid (8 mg, 0.064 mmol), diisopropylethylamine (0.018 mL, 0.11 mmol), 1-hydroxybenzotriazole (14 mg, 0.11 mmol) and lastly BOP reagent (34 mg, 0.076 mmol). The mixture was maintained at 25 °C for 4 h, then partitioned between $NaHCO_{3(aq)}$ and CH_2Cl_2, the

organic phase dried over anhydrous sodium sulfate, concentrated in vacuo and purified by preparative thin layer chromatography (500 micron SiO_2, 20X20 cm, 30% EtOAc-hexane) to provide the product which was characterized by ^1H NMR, HPLC and mass spectrometry (m/z: 394 (M^++1)).

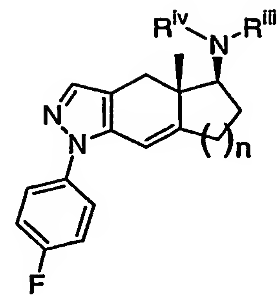
EXAMPLE 130



Sodium hydride (13 mg, 0.530 mmol) was tared, diluted with a THF (0.5 mL) solution of **EXAMPLE 129** (21 mg, 0.053 mmol) and then treated with allyl iodide (0.025 mL, 0.265 mmol). The mixture was maintained at 25 °C for 12 h, then partitioned between $NH_4Cl_{(aq)}$ and $CHCl_3$, the organic phase dried over anhydrous sodium sulfate, and concentrated in vacuo. The crude *N*-allyl amide was diluted into ethyl acetate (1 mL) and treated with catalytic 10% Pd-C. The system was fitted with a balloon of hydrogen gas, and the mixture stirred under an atmosphere of H_2 at 25 °C for 1 h. The mixture was then filtered over celite, washed with EtOAc, and the filtrate concentrated in vacuo. The residue was purified by preparative thin layer chromatography (500 micron SiO_2, 20X20 cm, 30% EtOAc-hexane) to provide the product which was characterized by ^1H NMR, HPLC and mass spectrometry (m/z: 436 (M^++1)).

EXAMPLES 131-209

The following compounds were prepared under conditions similar to those described in the examples above and illustrated in Schemes 4 and 5. Methyl iodide or methylamine hydrochloride was used in place of allyl iodide or *n*-propylamine hydrochloride respectively to generate the *N*-methyl analogs shown in the table below. For examples other than amides, a chloroformate or isocyanate or sulfonyl chloride was used to generate carbamates or ureas or sulfonamides respectively shown in the table below. The following examples were characterized by ^1H NMR, HPLC and mass spectrometry.



EX.	n	R^{iii} Group	R^{iv} Group	MS (m/z) (M^{+}+1)
131	1	CO(3,3,3-trifluoropropyl)	H	408
132	1	CO(2-(trifluoromethyl)phenyl)	H	456
133	1	CO(3-chlorophenyl)	H	422
134	1	$COCH_2$(2-(trifluoromethyl)phenyl)	H	470
135	1	CO(2,4,5-trifluorophenyl)	H	442
136	1	CO(3-thiopheneyl)	H	394
137	1	$COCH_2$(2,4-difluorophenyl)	H	438
138	1	$COCH_2$(3-chlorophenyl)	H	436
139	1	CO(3-chloro-4-fluorophenyl)	H	440
140	1	$COCH_2$(2,5-difluorophenyl)	H	438
141	1	$COCH_2$(2-thiopheneyl)	H	408
142	1	$COCH_2$(3-thiopheneyl)	H	408

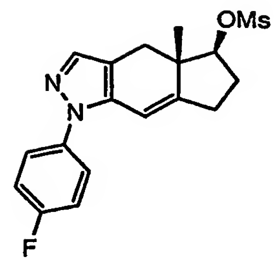
143	1	CO(2-chloro-5-fluorophenyl)	H	440
144	1	$COCH_2$(3-chloro-4-fluorophenyl)	H	454
145	1	CO(2,4,5-trifluorophenyl)	methyl	456
146	1	CO(2-(trifluoromethyl)phenyl)	methyl	470
147	1	CO(2-thiopheneyl)	methyl	408
148	1	CO(3-chlorophenyl)	methyl	436
149	1	CO(phenyl)	H	388
150	1	CO(2,4-difluorophenyl)	H	424
151	1	$COCH_2$(3-chloro-4-fluorophenyl)	methyl	468
152	1	CO(2,4-difluorophenyl)	methyl	438
153	1	$COCH_2$(2-(trifluoromethyl)phenyl)	methyl	484
154	1	CO(2-fluorophenyl)	H	406
155	1	CO(2,6-difluorophenyl)	H	424
156	1	CO(2-chlorophenyl)	H	422
157	1	CO(1-naphthyl)	H	438
158	1	CO(2-(trifluoromethyl)-4-fluorophenyl)	H	474
159	1	CO(2,5-difluorophenyl)	H	424

160	1	CO(2,3-difluorophenyl)	H	424
161	1	CO(2-chloro-4-fluorophenyl)	H	440
162	1	CO(2-chloro-3-fluorophenyl)	H	440
163	1	CO(tert-butyl)	H	368
164	1	CO(isopropyl)	H	354
165	1	CO(2-chloro-3-fluorophenyl)	methyl	454
166	1	CO(2-(trifluoromethyl)-4-fluorophenyl)	methyl	488
167	1	CO(2,6-difluorophenyl)	methyl	438
168	1	CO(2-chloro-4-fluorophenyl)	methyl	454
169	1	SO_2(phenyl)	H	424
170	1	CO(2,6-dichlorophenyl)	methyl	470
171	1	CO(2,6-dichlorophenyl)	H	456
172	2	CO(phenyl)	H	402
173	2	CO(2-(trifluoromethyl)phenyl)	H	470
174	2	CO(2-chloro-4-fluorophenyl)	H	454
175	2	CO(2-chlorophenyl)	H	436
176	2	CO(2-fluorophenyl)	H	420

177	2	$COCH_2$(2-(trifluoromethyl)phenyl)	H	484
178	2	$COCH_2$(2,4-difluorophenyl)	H	452
179	2	$COCH_2$(3-chlorophenyl)	H	450
180	1	SO_2(2,4-difluorophenyl)	H	460
181	1	CO(2,4-difluorophenyl)	*n*-propyl	466
182	1	SO_2(3-chlorophenyl)	H	458
183	2	CO(3-chlorophenyl)	H	436
184	1	SO_2(2-chloro-4-fluorophenyl)	H	476
185	1	CO_2(phenyl)	methyl	418
186	1	CO_2(phenyl)	H	404
187	1	CONH(phenyl)	H	403
188	1	SO_2(2-fluorophenyl)	H	442
189	1	SO_2(2-chlorophenyl)	H	458
190	1	CONH(phenyl)	methyl	417
191	1	SO_2(2-(trifluoromethyl)phenyl)	H	492
192	2	CONH(phenyl)	H	417
193	1	SO_2(3-fluorophenyl)	H	442

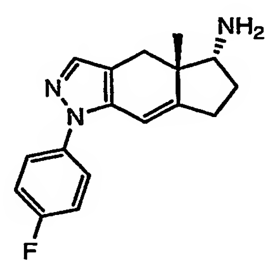
194	2	CO_2(phenyl)	H	418
195	2	CO(2,4-difluorophenyl)	H	438
196	1	CO(2-chloro-4-fluorophenyl)	*n*-propyl	482
197	2	CO(2-(trifluoromethyl)-4-fluorophenyl)	H	488
198	2	CO(2-chloro-4-fluorophenyl)	methyl	468
199	2	CO(2-(trifluoromethyl)-4-fluorophenyl)	methyl	502
200	2	CO(2,4-difluorophenyl)	methyl	452
201	1	CO(2-(trifluoromethyl)-4-fluorophenyl)	*n*-propyl	516
202	2	SO_2(2-chloro-4-fluorophenyl)	H	490
203	2	SO_2(2,4-difluorophenyl)	H	474
204	1	SO_2(3-chlorophenyl)	methyl	472
205	1	SO_2(2-chloro-4-fluorophenyl)	methyl	490
206	1	SO_2(3-chlorophenyl)	*n*-propyl	500
207	2	CO(2,4-difluorophenyl)	*n*-propyl	480
208	2	CO(2-chloro-4-fluorophenyl)	*n*-propyl	496
209	2	CO(2-(trifluoromethyl)-4-fluorophenyl)	*n*-propyl	530

EXAMPLE 210



COMPOUND A (300 mg, 1.06 mmol) was diluted into methanol (10 mL) and treated with sodium borohydride (40 mg, 1.06 mmol). The mixture was maintained at 23 °C for 1.5 h, then partitioned between $NH_4Cl_{(aq)}$ and methylene chloride, the organic phase dried over anhydrous sodium sulfate, and concentrated in vacuo. This alcohol intermediate (130 mg, 0.46 mmol) was diluted into CH_2Cl_2 (5 mL), cooled to -20 °C, treated with Et_3N (0.092 mL, 0.64 mmol) and then methanesulfonyl chloride (0.042 mL, 0.55 mmol). The mixture was stirred at -20 °C for 10 min, warmed to 23 °C and maintained for 1 h. The mixture was then quickly partitioned between cold $NH_4Cl_{(aq)}$ and methylene chloride, the organic phase dried over anhydrous sodium sulfate, and concentrated in vacuo. The crude product mesylate was of sufficient purity to be used in subsequent reactions and was characterized by ^{1}H NMR, HPLC and mass spectrometry (m/z: 363 (M^++1)).

EXAMPLE 211

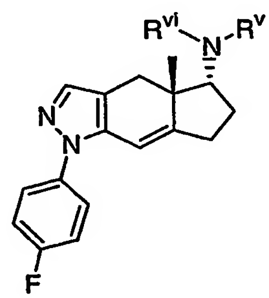


EXAMPLE 210 (64 mg, 0.177 mmol) was diluted into dimethyl acetamide (18 mL) and treated with sodium azide (530 mg, 8.16 mmol) followed by water (0.20 mL). The mixture was heated in a re-sealable pressure tube at 90 °C for 14 h, cooled to 23 °C, then partitioned between water and diethyl ether, the organic phase dried over anhydrous sodium sulfate, and concentrated in vacuo (DMAC remains). The crude product was purified by preparative reverse phase HPLC (C18 SiO_2, 0-100% acetonitrile gradient in water with 0.1% TFA eluent). The product azide intermediate (100 mg, 0.324 mmol) was diluted into ethyl acetate (4 mL) and treated with catalytic 10% Pd-C. The system was fitted with a balloon of hydrogen gas, and the mixture stirred under an atmosphere of H_2 at 25 °C for 30 min. The mixture was then filtered over celite,

washed with EtOAc, and the filtrate concentrated in vacuo to provide the pure amine product which was characterized by ^{1}H NMR, HPLC and mass spectrometry (m/z: 284 (M^++1)).

EXAMPLES 212-233

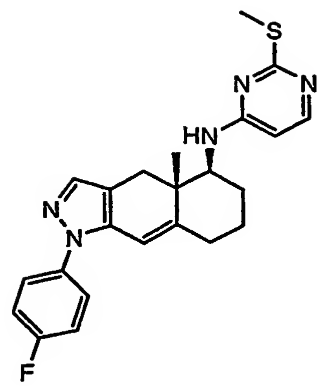
The following epimerized compounds were prepared under conditions similar to those described in the examples above and illustrated in Schemes 4-6. The following examples were characterized by ^{1}H NMR, HPLC and mass spectrometry.



EX.	R^v Group	R^{vi} Group	MS (m/z) (M^++1)
212	CO(phenyl)	H	388
213	SO_2(2-chloro-4-fluorophenyl)	H	476
214	CO(2-chlorophenyl)	H	422
215	CO(3-chlorophenyl)	H	422
216	CO(2-(trifluoromethyl)phenyl)	H	456
217	CO(isopropyl)	H	354
218	CO(tert-butyl)	H	368

219	CO(3-thiopheneyl)	H	394
220	CO(2-thiopheneyl)	H	394
221	CO(2,4,5-trifluorophenyl)	H	442
222	CO(2,5-difluorophenyl)	H	424
223	CO_2(phenyl)	H	404
224	SO_2(phenyl)	H	424
225	CO(2-chlorophenyl)	methyl	436
226	CO(2-(trifluoromethyl)phenyl)	methyl	470
227	CO(3-chlorophenyl)	methyl	436
228	CONH(phenyl)	H	403
229	CO(2,6-difluorophenyl)	H	424
230	$COCH_2$(2,4-difluorophenyl)	H	438
231	CO(2,4-difluorophenyl)	H	424
232	CO(2-fluorophenyl)	H	406
233	CO(2-(trifluoromethyl)-4-fluorophenyl)	*n*-propyl	516

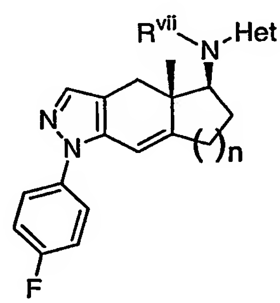
EXAMPLE 234



Using the procedure for the synthesis of **EXAMPLE 128, COMPOUND B** was transformed into the primary amine as shown in Scheme 7. This amine (20 mg, 0.067 mmol) was then combined with 4-chloro-2-methylthiopyrimidine (0.008 mL, 0.067 mmol), K_3PO_4 (286 mg, 1.35 mmol) and diluted into degassed toluene (0.7 mL) under an argon atmosphere. To this was added tris(dibenzylideneacetone)-dipalladium(0) (6 mg, 0.007 mmol) and (diphenylphosphino)ferrocene (7 mg, 0.014 mmol) and the resulting reaction mixture was heated to 100 °C for 15 hours. Upon cooling, the reaction mixture was filtered through celite, washed with methylene chloride and evaporated under reduced pressure. The crude product was purified by preparative thin layer chromatography (1000 micron SiO_2, 20X20 cm, 50% EtOAc-hexane) to provide the product which was characterized by ^1H NMR, HPLC and mass spectrometry (m/z: 422 (M^++1)).

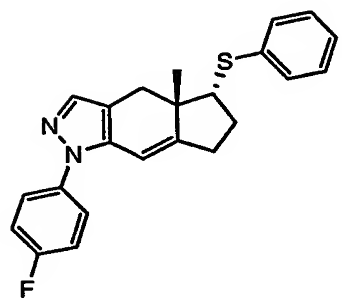
EXAMPLES 235-250

The following compounds were prepared under conditions similar to those described in the examples above and illustrated in Scheme 7. Installation of an R^{vii} Group (other than hydrogen shown in the table below) was accomplished using conditions described in **EXAMPLES 96-125.** The following examples were characterized by ^1H NMR, HPLC and mass spectrometry.



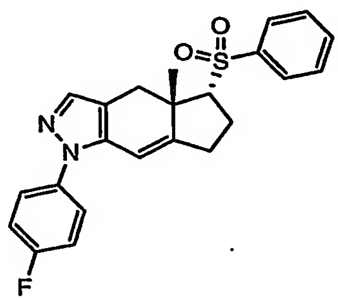
EX.	n	Het (Heterocycle)	R^{vii} Group	MS (m/z) (M^{+}+1)
235	1	2-pyridyl	H	361
236	1	4-isoquinolyl	H	411
237	1	2-(4-methyl)pyridyl	H	375
238	1	5-pyrimidyl	H	362
239	1	3-pyridyl	H	361
240	1	2-pyrimidyl	H	362
241	1	2-pyrimidyl	methyl	376
242	1	2-pyrimidyl	*n*-propyl	404
243	1	4-(2-methylthio)pyrimidyl	H	408
244	2	4-(2-methylthio)pyrimidyl	methyl	436
245	2	4-(2-methylthio)pyrimidyl	*n*-propyl	464
246	1	2-(4-trifluoromethyl)pyridyl	H	429
247	2	2-(4-trifluoromethyl)pyridyl	H	443
248	1	2-pyrazinyl	H	362
249	1	4-(2,3,5,6-tetrafluoro)pyridyl	H	433
250	2	4-(2,3,5,6-tetrafluoro)pyridyl	H	447

EXAMPLE 251



Cesium carbonate (46 mg, 0.141 mmol) was diluted into dry DMF (0.7 mL) and the solution was treated with benzene thiol (0.014 mL, 0.141 mmol). The reaction mixture was stirred at 23 °C for 20 min and then treated with a solution of **EXAMPLE 210** (17 mg, 0.047 mmol) in dry DMF (0.8 mL). The reaction mixture was then heated at 70 °C for 16 h, cooled to 23 °C, partitioned between EtOAc and $NaHCO_{3(aq)}$, the organic phase washed excessively with water to remove DMF, the organic phase dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by preparative reverse phase HPLC (C18 SiO_2, 0-100% acetonitrile gradient in water with 0.1% TFA eluent) to provide the product which was characterized by ^1H NMR, HPLC and mass spectrometry (m/z: 377 (M^++1)).

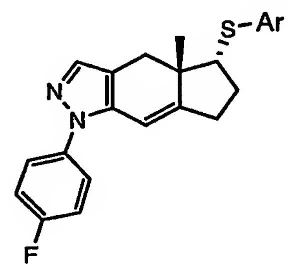
EXAMPLE 252



EXAMPLE 251 (4 mg, 0.011 mmol) was dissolved in methanol (0.4 mL), treated with a solution of oxone (14 mg, 0.022 mmol) in water (0.20 mL), and the reaction mixture vigorously stirred at 23 °C for 1.5 h. The methanol was removed under reduced pressure, and the remaining aqueous was extracted with methylene chloride. The organic phase was then dried over anhydrous sodium sulfate, and concentrated in vacuo to provide the pure product which was characterized by ^1H NMR, HPLC and mass spectrometry (m/z: 409 (M^++1)).

EXAMPLES 253-257

The following compounds were prepared under conditions similar to those described in the examples above and illustrated in Scheme 8. The following examples were characterized by ^{1}H NMR, HPLC and mass spectrometry.



EXAMPLE	Ar Group	MS (m/z) (M^++1)
253	2-chlorophenyl	411
254	3-chlorophenyl	411
255	2-(trifluoromethyl)phenyl	445
256	2,6-dichlorophenyl	445
257	2,4-dichlorophenyl	445

BIOLOGICAL ASSAYS

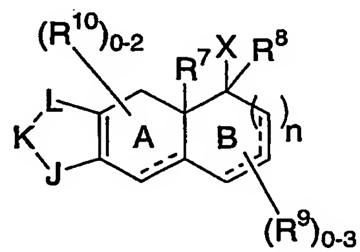
The activity of the compounds of the present invention regarding glucocorticoid receptor affinity can be evaluated using the following human GR binding assay:

GR Ligand Binding Assay

For the hGRI ligand binding assay, cytosols were prepared from recombinant baculovirus expressed receptors. Frozen cell pellets were dounce homogenized in ice cold KPO4 buffer (10mM KPO4, 20mM sodium molybdate, 1mM EDTA, 5mM DTT and complete protease inhibitor tablets from Boehringer Mannheim) with a "B" plunger. The homogenates were centrifuged at 35,000 x g for 1 h at 4°C in a JA-20 rotor. The IC50s were determined by incubating the cytosols at a final concentration of 2.5nM [1,2,4,6,7-^{3}H] Dexamethasone in the presence of increasing concentrations (10-11 to 10-6) of cold dexamethasone or the ligands at 4°C for 24 h. Bound and free were separated by a gel filtration assay, (Geissler et al,, personal communication). Half of the reaction was added to a gel filtration plate (MILLIPORE) containing sephadex G-25 beads that was previously equilibrated with KPO4 buffer containing 1mg/ml BSA and centrifuged at 1000 x g for 5 min.. The reaction plate was centrifuged at 1000 x g for 5 min. and the reactions were collected in a second 96-well plate and scintillation cocktail was added and counted in (Wallac) double coincidence beta counter. The IC50 values were calculated using a 4-parameter fit program. The compounds of this invention demonstrated a range of GR affinity in the above assay with IC50 values between 10 uM and 1 nM.

WHAT IS CLAIMED IS:

1. A compound represented by Formula I



I

or a pharmaceutically acceptable salt or hydrate thereof, wherein:

n is 0, 1 or 2;

J is selected from NR^1 or $C(R^1)(R^2)$;

K is selected from NR^3 or $C(R^3)(R^4)$;

L is selected from NR^5 or $C(R^5)(R^6)$;

X is selected from the group consisting of:-OR^a, -$N(R^b)$-Y-R^c or -$S(O)_j$-R^d, wherein:

Y is selected from a bond, –C(O)-, –C(O)–O–, wherein the point of attachment of the "–O–" group is to R^c forming an alkoxy moiety, -$S(O)_2$- and -C(O)-N(R^{12})-, wherein the point of attachment of the nitrogen group is to R^c, and

j is independently 0, 1 or 2,

R^a, R^b, R^c, R^d and R^8 are each independently selected from the group consisting of:

(1) hydrogen, except that R^d is not hydrogen and R^c is hydrogen only when Y is a bond or -C(O)-N(R^{12})-,

(2) C_{1-6}alkyl,

(3) C_{2-6}alkenyl,

(4) C_{2-6}alkynyl,

(5) C_{3-6}cycloalkyl,
(6) aryl,
(7) aralkyl,
(8) HET^1,
(9) -C_{1-6}alkyl-HET^2,
(10) aralkenyl,
(11) aralkynyl and
(12) arylsulfonylalkyl,

wherein items (2) to (5) above and the alkyl portions of items (7), (9) and (12) above and the alkenyl portion of item (10) above and the alkynyl portion of item (11) above are optionally substituted from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of: halo, oxo, OR^{11}, $N(R^{12})_2$, C_{3-6}cycloalkyl and C_{1-4}alkyl-$S(O)_m$-, wherein m is 0, 1 or 2, and

wherein items (6) and (8) above and the aryl portion of items (7), (10), (11) and (12) above and the HET^2 portion of item (9) above are optionally substituted from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of:

(a) halo,
(b) OR^{11},
(c) $N(R^{12})_2$,
(d) C_{1-6}alkyl,
(e) C_{2-6}alkenyl,
(f) C_{2-6}akynyl,
(g) C_{1-6}alkyl-$S(O)_p$-, wherein p is 0, 1 or 2,
(h) aryl,
(i) aryl-$S(O)_q$-, wherein q is 0, 1 or 2,
(j) HET^3,
(k) aralkyl,
(l) aroyl,
(m) aryloxy,
(n) aralkoxy and
(o) CN,

wherein items (d) to (g) above and the alkyl portions of item (k) above are optionally substituted from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of: halo, OR^{11} and $N(R^{12})_2$, and

wherein items (h), (i), (j), (l) and (m) above and the aryl portions of items (k) and (n) above are optionally substituted from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of: halo, OR^{12} and C_{1-4}alkyl,

R^1, R^2, R^3, R^4, R^5 and R^6 are each independently selected from the group consisting of:

(1) hydrogen,
(2) halo,
(3) C_{1-6}alkyl,
(4) C_{2-6}alkenyl,
(5) C_{2-6}akynyl,
(6) C_{3-6}cycloalkyl,
(7) C_{1-6}alkoxy,
(8) C_{1-6}alkyl-$S(O)_r$-, wherein r is 0, 1 or 2,
(9) aryl,
(10) aralkyl,
(11) HET^4 and
(12) -C_{1-6}alkyl-HET^5,

wherein items (3) to (8) above and the alkyl portions of items (10) and (12) above are optionally substituted from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of: halo, OR^{11}, $N(R^{12})_2$ and C_{1-6}alkyl-$S(O)_s$-, wherein s is 0, 1 or 2; and

wherein items (9) and (11) and the aryl portion of items (10) and the HET portion of item (12) are optionally substituted from one up to the maximum number of substituable positions with a substituent independently selected from the group consisting of:

(a) halo,
(b) OR^{11},
(c) $N(R^{12})_2$,
(d) C_{1-6}alkyl,
(e) C_{2-6}alkenyl,
(f) C_{2-6}akynyl and

(g) C_{1-6}alkyl-S(O)$_t$-, wherein t is 0, 1 or 2,

wherein items (d) to (g) above are optionally substituted with from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of: halo, OR^{11} and $N(R^{12})_2$,

or R^1 and R^3 or R^3 and R^5 may be joined together to form a double bond;

R^7 is selected from the group consisting of:

(1) hydrogen,
(2) OR^{11},
(3) C_{1-4}alkyl,
(4) aryl and
(5) aralkyl,

wherein item (3) above and the alkyl portion of item (5) above are optionally substituted with from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of: halo, OR^{11} and $N(R^{12})_2$, and

wherein item (4) above and the aryl portion of item (5) above are optionally substituted with from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of:

(a) halo,
(b) OR^{11},
(c) $N(R^{12})_2$,
(d) C_{1-6}alkyl,
(e) C_{2-6}alkenyl and
(f) C_{2-6}akynyl,

wherein items (d) to (f) above are optionally substituted with from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of: halo, OR^{11} and $N(R^{12})_2$;

each R^9 and R^{10} is independently selected from the group consisting of:

(1) halo,
(2) C_{1-6}alkyl,
(3) C_{2-6}alkenyl,
(4) C_{1-6}alkoxy and

(5) hydroxy,

wherein items (2) to (4) above are optionally substituted from one up to the maximum number of substitutable positions with a substituent independently selected from the group consisting of: halo, OR^{12}, $N(R^{11})_2$ and C_{1-6}alkyl-$S(O)_u$-, wherein u is 0, 1 or 2;

each R^{11} and R^{12} is independently selected from the group consisting of hydrogen and C_{1-4}alkyl, optionally substituted from one up to the maximum number of substitutable positions with halo; and

HET^1, HET^2, HET^3, HET^4 and HET^5 are each independently selected from the group of heterocycles consisting of: benzimidazolyl, benzofuranyl, benzopyrazolyl, benzotriazolyl, benzothiophenyl, benzoxazolyl, carbazolyl, carbolinyl, cinnolinyl, furanyl, imidazolyl, indolinyl, indolyl, indolazinyl, indazolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthyridinyl, oxadiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridopyridinyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, quinazolinyl, quinolyl, quinoxalinyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, azetidinyl, 1,4-dioxanyl, hexahydroazepinyl, piperazinyl, piperidinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, dihydrobenzimidazolyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, dihydrobenzoxazolyl, dihydrofuranyl, dihydroimidazolyl, dihydroindolyl, dihydroisooxazolyl, dihydroisothiazolyl, dihydrooxadiazolyl, dihydrooxazolyl, dihydropyrazinyl, dihydropyrazolyl, dihydropyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dihydroquinolinyl, dihydrotetrazolyl, dihydrothiadiazolyl, dihydrothiazolyl, dihydrothienyl, dihydrotriazolyl, dihydroazetidinyl, methylenedioxybenzoyl, tetrahydrofuranyl, and tetrahydrothienyl.

2. The compound according to Claim 1 wherein:

J is NR^1;

K is NR^3;

L is $C(R^5)(R^6)$; and

R^3 and R^5 are joined together to form a double bond.

3. The compound according to Claim 1 wherein the optional double bond shown in ring A of the compound of Formula I is present.

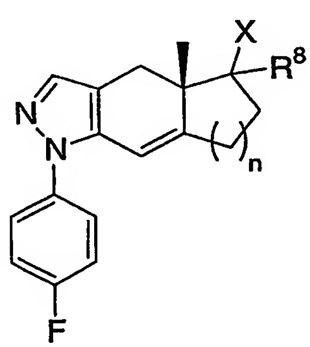
4. The compound according to Claim 1 wherein X is $-OR^a$.

5. The compound according to Claim 1 wherein X is $-N(R^b)-Y-R^c$, wherein Y is selected from $-C(O)-$, $-C(O)-O-$, wherein the point of attachment of the "–O–" group is to R^c forming an alkoxy moiety, $-S(O)_2-$ and $-C(O)-N(R^{12})-$, wherein the point of attachment of the nitrogen group is to R^c.

6. The compound according to Claim 1 wherein X is $-S(O)_j-R^d$.

7. The compound according to Claim 1 wherein n is 0 and the optional double bonds shown in ring B are not present.

8. A compound according to Claim 1 of Formula II:



II

or a pharmaceutically acceptable salt or hydrate thereof, wherein:

X is selected from the group consisting of: $-OR^a$, $-N(R^b)-Y-R^c$, $-S(O)_j-R^d$, wherein:

Y is selected from a bond, $-C(O)-$, $-C(O)-O-$, wherein the point of attachment of the "–O–" group is to R^c forming an alkoxy moiety, $-S(O)_2-$ and $-C(O)-N(R^{12})-$, wherein the point of attachment of the nitrogen group is to R^c, and

j is 0, 1 or 2,

n is 1 or 2,

R^a, R^b, R^c, R^d and R^8 are each independently selected from the group consisting of:

(1) hydrogen, except that R^d is not hydrogen and R^c is hydrogen only when Y is a bond or -C(O)-N(R^{12})-,

(2) C_{1-6}alkyl,

(3) C_{2-6}alkenyl,

(4) C_{2-6}akynyl,

(5) C_{3-6}cycloalkyl,

(6) aryl,

(7) aralkyl,

(8) HET^1,

(9) -C_{1-6}alkyl-HET^2,

(10) aralkenyl,

(11) aralkynyl and

(12) arylsulfonylalkyl,

wherein items (2) to (5) above and the alkyl portions of items (7), (9) and (12) above and the alkenyl portion of item (10) above and the alkynyl portion of item (11) above are optionally substituted with oxo and optionally substituted with one to three substituents independently selected from the group consisting of: halo, OR^{11}, $N(R^{12})_2$, C_{3-6}cycloalkyl and C_{1-4}alkyl-$S(O)_m$-, wherein m is 0, 1 or 2, and

wherein items (6) and (8) above and the aryl portion of items (7), (10), (11) and (12) above and the HET^2 portion of item (9) above are optionally substituted with one to five substituents independently selected from the group consisting of:

(a) halo,

(b) OR^{11},

(c) $N(R^{12})_2$,

(d) C_{1-6}alkyl,

(e) C_{2-6}alkenyl,

(f) C_{2-6}akynyl,

(g) C_{1-6}alkyl-$S(O)_p$-, wherein p is 0, 1 or 2,

(h) aryl,

(i) aryl-$S(O)_q$-, wherein q is 0, 1 or 2,

(j) HET^3,
(k) aralkyl,
(l) aroyl,
(m) aryloxy,
(n) aralkoxy and
(o) CN,

wherein items (d) to (g) above and the alkyl portions of item (k) above are optionally substituted with one to three substituents independently selected from the group consisting of: halo, OR^{11} and $N(R^{12})_2$, and

wherein items (h), (i), (j), (l) and (m) above and the aryl portions of items (k) and (n) above are optionally substituted with one to three substituents independently selected from the group consisting of: halo, OR^{12} and C_{1-4}alkyl,

each R^{11} and R^{12} is independently selected from the group consisting of hydrogen and C_{1-4}alkyl, optionally substituted with 1 to 3 halo groups; and

HET^1, HET^2 and HET^3 are each independently selected from the group of heterocycles consisting of: benzimidazolyl, benzofuranyl, benzopyrazolyl, benzotriazolyl, benzothiophenyl, benzoxazolyl, carbazolyl, carbolinyl, cinnolinyl, furanyl, imidazolyl, indolinyl, indolyl, indolazinyl, indazolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthyridinyl, oxadiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridopyridinyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, quinazolinyl, quinolyl, quinoxalinyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, azetidinyl, 1,4-dioxanyl, hexahydroazepinyl, piperazinyl, piperidinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, dihydrobenzimidazolyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, dihydrobenzoxazolyl, dihydrofuranyl, dihydroimidazolyl, dihydroindolyl, dihydroisooxazolyl, dihydroisothiazolyl, dihydrooxadiazolyl, dihydrooxazolyl, dihydropyrazinyl, dihydropyrazolyl, dihydropyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dihydroquinolinyl, dihydrotetrazolyl, dihydrothiadiazolyl, dihydrothiazolyl, dihydrothienyl, dihydrotriazolyl, dihydroazetidinyl, methylenedioxybenzoyl, tetrahydrofuranyl, and tetrahydrothienyl.

9. The compound according to Claim 8 wherein

X is $-OR^a$

n is 1, and

R^a is selected from the group consisting of:

(1) hydrogen,
(2) acetyl,
(3) benzyl,
(4) C_{1-6}alkyl,
(5) C_{2-6}alkenyl,
(6) C_{2-6}alkynyl and
(7) C_{3-6}cycloalkyl,

R^8 is selected from the group consisting of:

(1) hydrogen,
(2) C_{1-6}alkyl,
(3) C_{2-6}alkenyl,
(4) C_{2-6}akynyl,
(5) C_{3-6}cycloalkyl,
(6) aryl,
(7) aralkyl,
(8) HET^1,
(9) -C_{1-6}alkyl-HET^2,
(10) aralkenyl,
(11) aralkynyl, and
(12) arylsulfonylalkyl

wherein items (2) to (5) above and the alkyl portions of items (7), (9) and (12) above and the alkenyl portion of item (10) above and the alkynyl portion of item (11) above are optionally substituted with oxo and optionally substituted with one to three substituents independently selected from the group consisting of: halo, OR^{11} and C_{3-6}cycloalkyl,

wherein items (6) and (8) above and aryl portion of items (7), (10), (11) and (12) above and the HET^2 portion of item (9) above are optionally substituted with one to five substituents independently selected from the group consisting of:

(a) halo,
(b) C_{1-6}alkyl,
(c) C1-4alkoxy and

(d) aryl,

R^{11} is selected from the group consisting of hydrogen and C_{1-4}alkyl, optionally substituted with 1 to 3 halo groups; and

HET^1 and HET^2 are each independently selected from the group of heterocycles consisting of: benzimidazolyl, benzofuranyl, benzopyrazolyl, benzotriazolyl, benzothiophenyl, benzoxazolyl, carbazolyl, carbolinyl, cinnolinyl, furanyl, imidazolyl, indolinyl, indolyl, indolazinyl, indazolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthyridinyl, oxadiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridopyridinyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, quinazolinyl, quinolyl, quinoxalinyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, azetidinyl, 1,4-dioxanyl, hexahydroazepinyl, piperazinyl, piperidinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, dihydrobenzimidazolyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, dihydrobenzoxazolyl, dihydrofuranyl, dihydroimidazolyl, dihydroindolyl, dihydroisooxazolyl, dihydroisothiazolyl, dihydrooxadiazolyl, dihydrooxazolyl, dihydropyrazinyl, dihydropyrazolyl, dihydropyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dihydroquinolinyl, dihydrotetrazolyl, dihydrothiadiazolyl, dihydrothiazolyl, dihydrothienyl, dihydrotriazolyl, dihydroazetidinyl, methylenedioxybenzoyl, tetrahydrofuranyl, and tetrahydrothienyl.

10. The compound according to Claim 9 wherein:

R^8 is selected from the group consisting of:

(1) hydrogen,
(2) C_{1-6}alkyl,
(3) C_{2-6}alkenyl,
(4) C_{2-6}akynyl,
(5) C_{3-6}cycloalkyl,
(6) phenyl or naphthyl,
(7) benzyl or phenethyl,
(8) benzothiophene,
(9) phenylethenyl,
(10) phenylethynyl, and
(11) phenylsulfonylmethyl,

wherein items (2) to (5) above are optionally substituted with one to three substituents independently selected from the group consisting of: halo, OR^{11} and C_{3-6}cycloalkyl,

wherein item (6) above and the phenyl portions of items (7), (9), (10) and (11) above are optionally substituted with one to five substituents independently selected from the group consisting of:

(a) halo,
(b) C_{1-6}alkyl,
(c) C_{1-4}alkoxy and
(d) phenyl.

11. The compound according to Claim 8 wherein:

X is -N(R^b)-Y-R^c, wherein:

Y is selected from –C(O)-, –C(O)–O–, wherein the point of attachment of the "–O–" group is to R^c forming an alkoxy moiety, -S(O)$_2$- and -C(O)-N(R^{12})-, wherein the point of attachment of the nitrogen group is to R^c, and

n is 1,

R^8 is hydrogen, and

R^b and R^c are each independently selected from the group consisting of:

(1) hydrogen, except that R^c is not hydrogen,
(2) C_{1-6}alkyl,
(3) C_{2-6}alkenyl,
(4) C_{2-6}akynyl,
(5) C_{3-6}cycloalkyl,
(6) aryl,
(7) aralkyl,
(8) HET^1,
(9) -C_{1-6}alkyl-HET^2,
(10) aralkenyl,
(11) aralkynyl and
(12) arylsulfonylalkyl,

wherein items (2) to (5) above and the alkyl portions of items (7), (9) and (12) above and the alkenyl portion of item (10) above and the alkynyl portion of item (11) above are optionally substituted with oxo and optionally substituted with with one to three substituents independently selected from the group consisting of: halo, OR^{11}, $N(R^{12})_2$, C_{3-6}cycloalkyl and C_{1-4}alkyl-$S(O)_m$-, wherein m is 0, 1 or 2, and

wherein items (6) and (8) above and the aryl portion of items (7), (10), (11) and (12) above and the HET^2 portion of item (9) above are optionally substituted with one to five substituents independently selected from the group consisting of:

(a) halo,
(b) OR^{11},
(c) $N(R^{12})_2$,
(d) C_{1-6}alkyl,
(e) C_{2-6}alkenyl,
(f) C_{2-6}akynyl,
(g) C_{1-6}alkyl-$S(O)_p$-, wherein p is 0, 1 or 2,
(h) aryl,
(i) aryl-$S(O)_q$-, wherein q is 0, 1 or 2,
(j) HET^3,
(k) aralkyl,
(l) aroyl,
(m) aryloxy,
(n) aralkoxy and
(o) CN,

wherein items (d) to (g) above and the alkyl portions of item (k) above are optionally substituted with one to three substituents independently selected from the group consisting of: halo, OR^{11} and $N(R^{12})_2$, and

wherein items (h), (i), (j), (l) and (m) above and the aryl portions of items (k) and (n) above are optionally substituted with one to three substituents independently selected from the group consisting of: halo, OR^{12} and C_{1-4}alkyl,

each R^{11} and R^{12} is independently selected from the group consisting of hydrogen and C_{1-4}alkyl, optionally substituted with 1 to 3 halo groups; and

HET^1, HET^2 and HET^3 are each independently selected from the group of heterocycles consisting of: benzimidazolyl, benzofuranyl, benzopyrazolyl, benzotriazolyl, benzothiophenyl, benzoxazolyl, carbazolyl, carbolinyl, cinnolinyl, furanyl, imidazolyl, indolinyl, indolyl, indolazinyl, indazolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthyridinyl, oxadiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridopyridinyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, quinazolinyl, quinolyl, quinoxalinyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, azetidinyl, 1,4-dioxanyl, hexahydroazepinyl, piperazinyl, piperidinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, dihydrobenzimidazolyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, dihydrobenzoxazolyl, dihydrofuranyl, dihydroimidazolyl, dihydroindolyl, dihydroisooxazolyl, dihydroisothiazolyl, dihydrooxadiazolyl, dihydrooxazolyl, dihydropyrazinyl, dihydropyrazolyl, dihydropyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dihydroquinolinyl, dihydrotetrazolyl, dihydrothiadiazolyl, dihydrothiazolyl, dihydrothienyl, dihydrotriazolyl, dihydroazetidinyl, methylenedioxybenzoyl, tetrahydrofuranyl, and tetrahydrothienyl.

12. The compound according to Claim 11 wherein:

R^b and R^c are each independently selected from the group consisting of:

(1) hydrogen, except that R^c is hydrogen only when Y is a bond or -C(O)-N(R^{12})-,

(2) C_{1-6}alkyl,
(3) C_{2-6}alkenyl,
(4) C_{2-6}akynyl,
(5) C_{3-6}cycloalkyl,
(6) aryl,
(7) aralkyl,
(8) HET^1,
(9) -C_{1-6}alkyl-HET^2,
(10) aralkenyl, and
(11) aralkynyl,

wherein items (2) to (5) above are optionally substituted with 1-3 halo groups, and

wherein items (6) and (8) and aryl portion of items (7), (10) and (11) above and the HET2 portion of item (9) above are optionally substituted with one to five substituents independently selected from the group consisting of:

(a) halo,

(b) C_{1-4}alkyl, optionally substituted with 1-3 halo groups, and

(c) C_{1-4}alkylthio,

HET1 and HET2 are each independently selected from the group of heterocycles consisting of: benzimidazolyl, benzofuranyl, benzopyrazolyl, benzotriazolyl, benzothiophenyl, benzoxazolyl, carbazolyl, carbolinyl, cinnolinyl, furanyl, imidazolyl, indolinyl, indolyl, indolazinyl, indazolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthyridinyl, oxadiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridopyridinyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, quinazolinyl, quinolyl, quinoxalinyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, azetidinyl, 1,4-dioxanyl, hexahydroazepinyl, piperazinyl, piperidinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, dihydrobenzimidazolyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, dihydrobenzoxazolyl, dihydrofuranyl, dihydroimidazolyl, dihydroindolyl, dihydroisooxazolyl, dihydroisothiazolyl, dihydrooxadiazolyl, dihydrooxazolyl, dihydropyrazinyl, dihydropyrazolyl, dihydropyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dihydroquinolinyl, dihydrotetrazolyl, dihydrothiadiazolyl, dihydrothiazolyl, dihydrothienyl, dihydrotriazolyl, dihydroazetidinyl, methylenedioxybenzoyl, tetrahydrofuranyl, and tetrahydrothienyl.

13. The compound according to Claim 12 wherein:

R^b is selected from the group consisting of: hydrogen and C_{1-4}alkyl, and

R^c is selected from the group consisting of:

(1) C_{1-4}alkyl,

(2) phenyl or benzyl, each optionally substituted with 1 to 5 groups independently selected from fluoro, chloro and trifluoromethyl,

(3) naphthyl,

(4) thiopheneyl,

(5) pyridyl,

(6) isoquinolyl,

(7) pyrimidyl and

(8) pyrazyl,

wherein items (4) to (8) above are optionally substitited with 1 to 5 groups independently selected from fluoro, chloro, methyl,methylthio and trifluoromethyl.

14. The compound according to Claim 13, wherein R^c is phenyl, optionally substituted with 1 to 5 groups independently selected from fluoro, chloro and trifluoromethyl.

15. The compound according to Claim 8, wherein:

X is $-S(O)_j-R^d$, wherein j is 0, 1 or 2,

n is 1,

R^8 is hydrogen, and

R^d is selected from the group consisting of:

(1) C_{1-6}alkyl,
(2) C_{2-6}alkenyl,
(3) C_{2-6}akynyl,
(4) C_{3-6}cycloalkyl,
(5) aryl,
(6) aralkyl,
(7) HET^1,
(8) $-C_{1-6}$alkyl-HET^2,
(9) aralkenyl, and
(10) aralkynyl,

wherein items (1) to (4) above are optionally substituted with 1-3 halo groups, and

wherein items (5) and (7) and aryl portion of items (6), (9) and (10) above and the HET^2 portion of item (8) above are optionally substituted with one to five substituents independently selected from the group consisting of:

(a) halo,
(b) C_{1-4}alkyl, optionally substituted with 1-3 halo groups, and
(c) C_{1-4}alkylthio, and

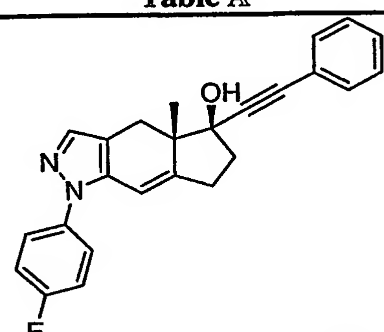
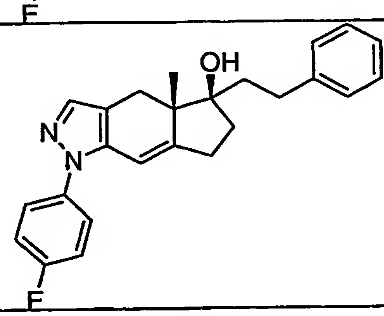
HET1 and HET2 are each independently selected from the group of heterocycles consisting of: benzimidazolyl, benzofuranyl, benzopyrazolyl, benzotriazolyl, benzothiophenyl, benzoxazolyl, carbazolyl, carbolinyl, cinnolinyl, furanyl, imidazolyl, indolinyl, indolyl, indolazinyl, indazolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthyridinyl, oxadiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridopyridinyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, quinazolinyl, quinolyl, quinoxalinyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, azetidinyl, 1,4-dioxanyl, hexahydroazepinyl, piperazinyl, piperidinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, dihydrobenzimidazolyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, dihydrobenzoxazolyl, dihydrofuranyl, dihydroimidazolyl, dihydroindolyl, dihydroisooxazolyl, dihydroisothiazolyl, dihydrooxadiazolyl, dihydrooxazolyl, dihydropyrazinyl, dihydropyrazolyl, dihydropyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dihydroquinolinyl, dihydrotetrazolyl, dihydrothiadiazolyl, dihydrothiazolyl, dihydrothienyl, dihydrotriazolyl, dihydroazetidinyl, methylenedioxybenzoyl, tetrahydrofuranyl, and tetrahydrothienyl.

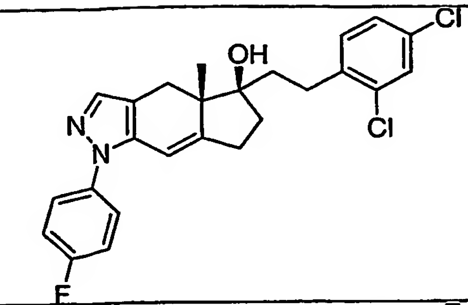
16. The compound according to Claim 15, wherein

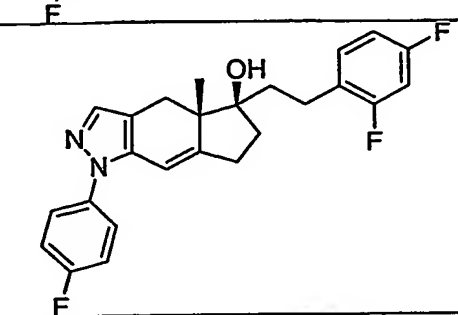
Rd is phenyl, optionally substituted with 1 to 5 groups independently selected from fluoro, chloro and trifluoromethyl.

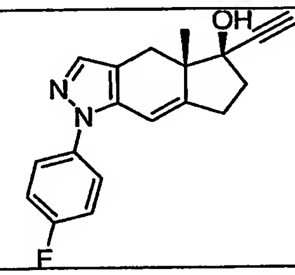
17. A compound selected from the following group:

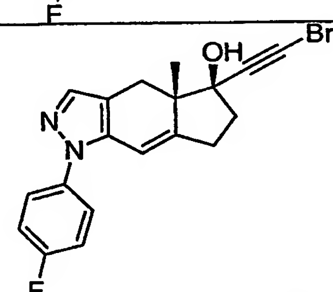
Table A

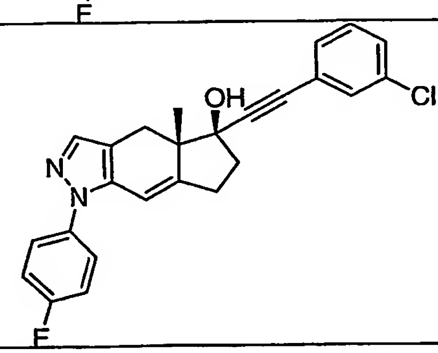













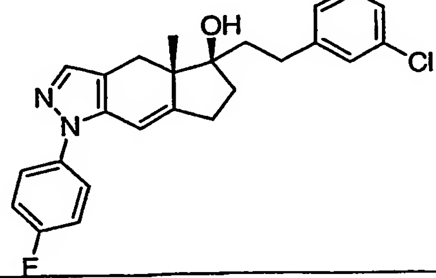
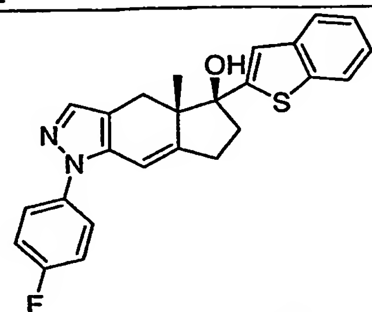
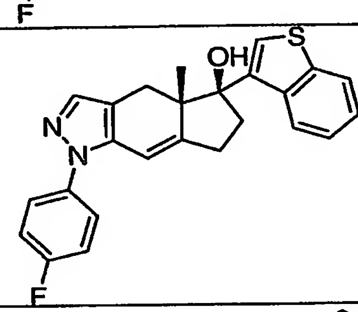
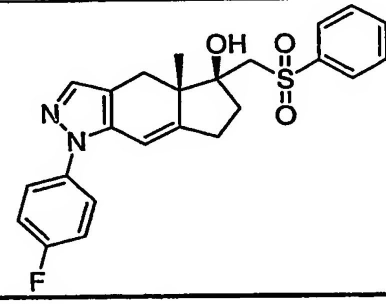
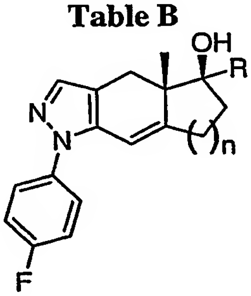





Table B

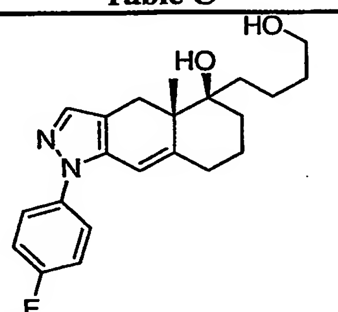
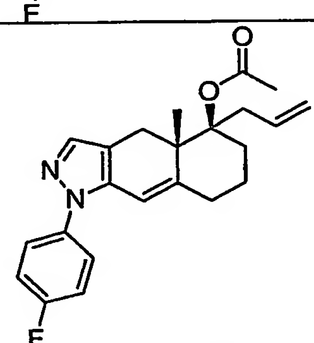
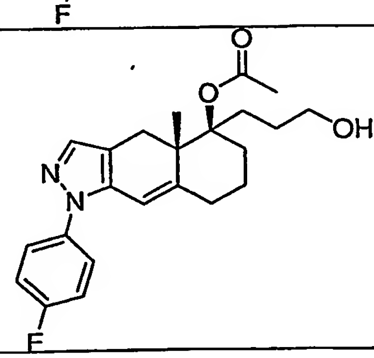


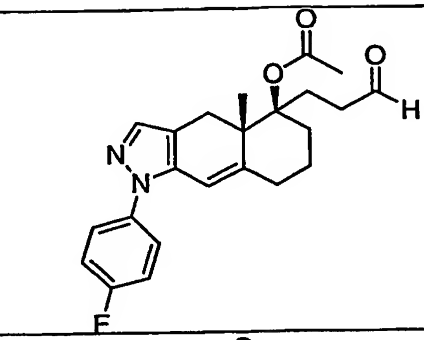
n	R Group
1	vinyl
2	vinyl
1	allyl
2	allyl
1	3-butenyl
2	3-butenyl
2	*n*-butyl
1	*n*-pentyl
2	*n*-pentyl
2	*n*-hexyl
1	3-methylbutyl
2	3-methylbutyl
1	2-cyclohexylethyl
2	2-cyclohexylethyl
1	3,3-dimethylbutyl
2	3,3-dimethylbutyl
1	4-methyl-3-pentenyl
2	4-methyl-3-pentenyl
1	4,4,4-trifluorobutyl
2	4,4,4-trifluorobutyl
1	3,4,4-trifluoro-3-butenyl
2	3,4,4-trifluoro-3-butenyl
1	3-methoxypropyl
2	3-methoxypropyl
2	benzyl
2	phenyl
2	phenethyl
2	3-phenylpropyl
1	2-(2-chlorophenyl)ethyl
2	2-(2-chlorophenyl)ethyl
2	2-(3-chlorophenyl)ethyl
1	2-(4-chlorophenyl)ethyl

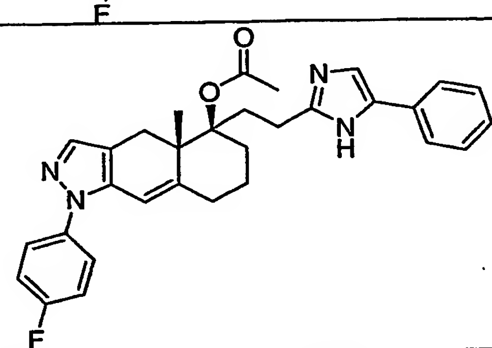
2	2-(4-chlorophenyl)ethyl
2	2-(2,4-dichlorophenyl)ethyl
1	2-(4-fluorophenyl)ethyl
2	2-(4-fluorophenyl)ethyl
1	2-(2,5-difluorophenyl)ethyl
1	2-(2,3-difluorophenyl)ethyl
1	2-(3,5-difluorophenyl)ethyl
1	2-(4-methoxyphenyl)ethyl
2	2-(4-methoxyphenyl)ethyl
1	2-(2-naphthyl)ethyl
2	2-(2-naphthyl)ethyl
2	2-(2,4-difluorophenyl)ethyl
1	2-(3-(trifluoromethyl)phenyl)ethyl
2	2-(3-(trifluoromethyl)phenyl)ethyl
1	2-(2-methoxyphenyl)ethyl
2	2-(2-methoxyphenyl)ethyl
1	2-(4-*tert*-butylphenyl)ethyl
2	2-(4-*tert*-butylphenyl)ethyl
1	2-(4-methylphenyl)ethyl
2	2-(4-methylphenyl)ethyl
1	2-(1-naphthyl)ethyl
2	2-(1-naphthyl)ethyl
1	2-(2-methylphenyl)ethyl
2	2-(2-methylphenyl)ethyl
1	2-(3-methylphenyl)ethyl
2	2-(3-methylphenyl)ethyl
1	2-(2-fluorophenyl)ethyl
1	2-(3-fluorophenyl)ethyl
1	2-(3,4-dichlorophenyl)ethyl
1	2-(2-chloro-4-fluorophenyl)ethyl
1	2-(3-thiopheneyl)ethyl
1	3-(*N*-pyrrolyl)propyl
2	3-(*N*-pyrrolyl)propyl
1	*E*-2-phenylethenyl

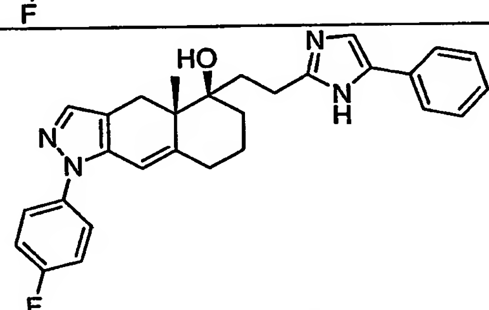
2	*E*-2-phenylethenyl
1	*Z*-2-phenylethenyl
2	*Z*-2-phenylethenyl
2	2-phenylethynyl
1	2-(2,4-difluorophenyl)ethynyl
1	2-(2-thiopheneyl)ethyl
1	2-(3,4-difluorophenyl)ethyl
1	2-(3,4,5-trifluorophenyl)ethyl
2	H
1	H

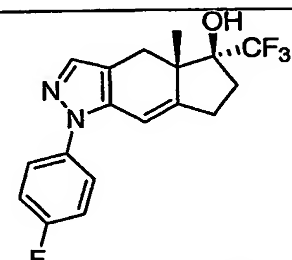
Table C

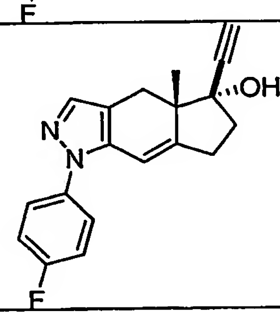




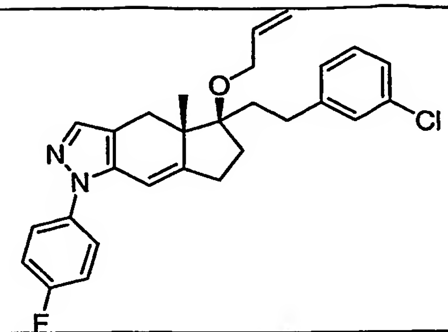












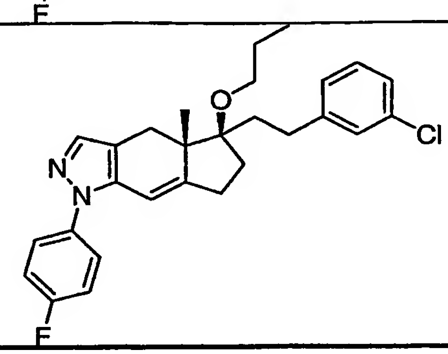
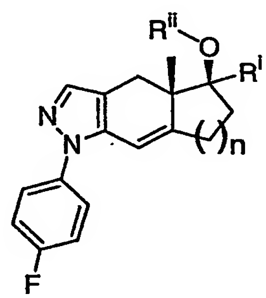


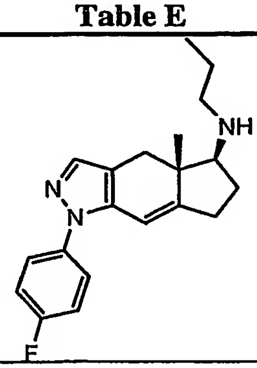
Table D



n	R^{i} Group	R^{ii} Group
1	H	*n*-propyl
2	allyl	allyl
1	phenethyl	cyclopropylmethyl
1	phenethyl	*E*-2-butenyl
1	2-(2,4-dichlorophenyl)ethyl	methyl
1	2-(2-chlorophenyl)ethyl	methyl
1	2-(3-chlorophenyl)ethyl	methyl
1	*n*-pentyl	methyl

1	2-(4-fluorophenyl)ethyl	methyl
2	phenethyl	methyl
1	2-(2,4-dichlorophenyl)ethyl	benzyl
1	2-(2,4-dichlorophenyl)ethyl	allyl
1	2-(2,4-dichlorophenyl)ethyl	*n*-propyl
1	2-(2-chlorophenyl)ethyl	*n*-propyl
1	phenethyl	*n*-propyl
1	phenethyl	methyl
1	2-(3-chlorophenyl)ethynyl	allyl
1	2-(3-chlorophenyl)ethynyl	*n*-propyl
1	2-(2,4-difluorophenyl)ethyl	methyl
2	2-(2,4-difluorophenyl)ethyl	methyl
1	phenethyl	*E*-2-pentenyl
1	trifluoromethyl	allyl
1	trifluoromethyl	*n*-propyl
1	2-(3-methylphenyl)ethyl	methyl
1	phenethyl	*n*-butyl
1	phenethyl	*n*-pentyl
1	2-(3,4-difluorophenyl)ethyl	*n*-propyl
1	2-(3-fluorophenyl)ethyl	methyl

Table E



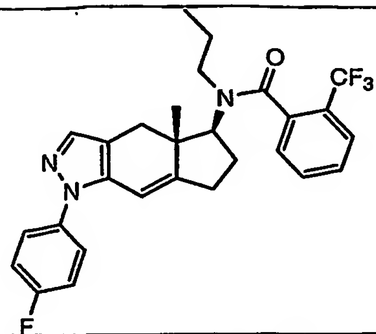
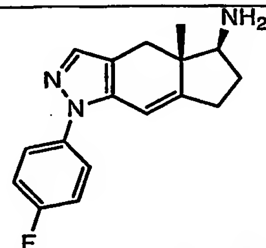
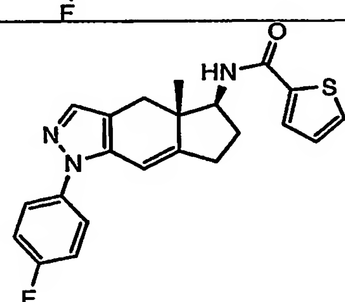
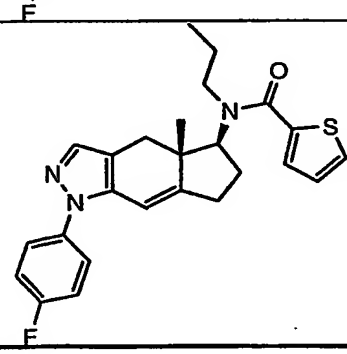
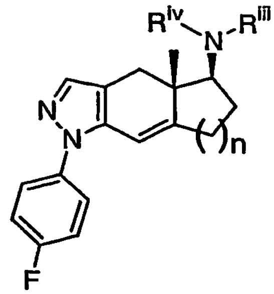





Table F



n	R^{iii} Group	R^{iv} Group
1	CO(3,3,3-trifluoropropyl)	H
1	CO(2-(trifluoromethyl)phenyl)	H
1	CO(3-chlorophenyl)	H
1	$COCH_2$(2-(trifluoromethyl)phenyl)	H
1	CO(2,4,5-trifluorophenyl)	H
1	CO(3-thiopheneyl)	H
1	$COCH_2$(2,4-difluorophenyl)	H
1	$COCH_2$(3-chlorophenyl)	H
1	CO(3-chloro-4-fluorophenyl)	H
1	$COCH_2$(2,5-difluorophenyl)	H
1	$COCH_2$(2-thiopheneyl)	H
1	$COCH_2$(3-thiopheneyl)	H
1	CO(2-chloro-5-fluorophenyl)	H
1	$COCH_2$(3-chloro-4-fluorophenyl)	H
1	CO(2,4,5-trifluorophenyl)	methyl
1	CO(2-(trifluoromethyl)phenyl)	methyl
1	CO(2-thiopheneyl)	methyl
1	CO(3-chlorophenyl)	methyl
1	CO(phenyl)	H
1	CO(2,4-difluorophenyl)	H
1	$COCH_2$(3-chloro-4-fluorophenyl)	methyl
1	CO(2,4-difluorophenyl)	methyl
1	$COCH_2$(2-(trifluoromethyl)phenyl)	methyl
1	CO(2-fluorophenyl)	H
1	CO(2,6-difluorophenyl)	H
1	CO(2-chlorophenyl)	H

1	CO(1-naphthyl)	H
1	CO(2-(trifluoromethyl)-4-fluorophenyl)	H
1	CO(2,5-difluorophenyl)	H
1	CO(2,3-difluorophenyl)	H
1	CO(2-chloro-4-fluorophenyl)	H
1	CO(2-chloro-3-fluorophenyl)	H
1	CO(tert-butyl)	H
1	CO(isopropyl)	H
1	CO(2-chloro-3-fluorophenyl)	methyl
1	CO(2-(trifluoromethyl)-4-fluorophenyl)	methyl
1	CO(2,6-difluorophenyl)	methyl
1	CO(2-chloro-4-fluorophenyl)	methyl
1	SO_2(phenyl)	H
1	CO(2,6-dichlorophenyl)	methyl
1	CO(2,6-dichlorophenyl)	H
2	CO(phenyl)	H
2	CO(2-(trifluoromethyl)phenyl)	H
2	CO(2-chloro-4-fluorophenyl)	H
2	CO(2-chlorophenyl)	H
2	CO(2-fluorophenyl)	H
2	$COCH_2$(2-(trifluoromethyl)phenyl)	H
2	$COCH_2$(2,4-difluorophenyl)	H
2	$COCH_2$(3-chlorophenyl)	H
1	SO_2(2,4-difluorophenyl)	H
1	CO(2,4-difluorophenyl)	*n*-propyl
1	SO_2(3-chlorophenyl)	H
2	CO(3-chlorophenyl)	H
1	SO_2(2-chloro-4-fluorophenyl)	H
1	CO_2(phenyl)	methyl
1	CO_2(phenyl)	H
1	CONH(phenyl)	H
1	SO_2(2-fluorophenyl)	H
1	SO_2(2-chlorophenyl)	H
1	CONH(phenyl)	methyl

1	SO_2(2-(trifluoromethyl)phenyl)	H
2	CONH(phenyl)	H
1	SO_2(3-fluorophenyl)	H
2	CO_2(phenyl)	H
2	CO(2,4-difluorophenyl)	H
1	CO(2-chloro-4-fluorophenyl)	*n*-propyl
2	CO(2-(trifluoromethyl)-4-fluorophenyl)	H
2	CO(2-chloro-4-fluorophenyl)	methyl
2	CO(2-(trifluoromethyl)-4-fluorophenyl)	methyl
2	CO(2,4-difluorophenyl)	methyl
1	CO(2-(trifluoromethyl)-4-fluorophenyl)	*n*-propyl
2	SO_2(2-chloro-4-fluorophenyl)	H
2	SO_2(2,4-difluorophenyl)	H
1	SO_2(3-chlorophenyl)	methyl
1	SO_2(2-chloro-4-fluorophenyl)	methyl
1	SO_2(3-chlorophenyl)	*n*-propyl
2	CO(2,4-difluorophenyl)	*n*-propyl
2	CO(2-chloro-4-fluorophenyl)	*n*-propyl
2	CO(2-(trifluoromethyl)-4-fluorophenyl)	*n*-propyl

Table G

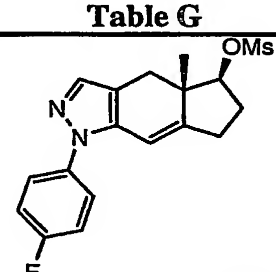
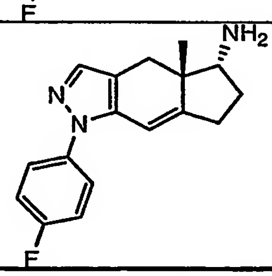
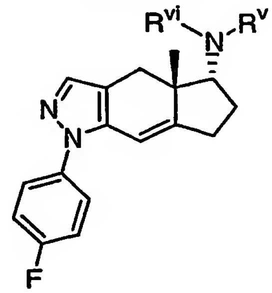



Table H



R^v Group	R^{vi} Group
CO(phenyl)	H
SO_2(2-chloro-4-fluorophenyl)	H
CO(2-chlorophenyl)	H
CO(3-chlorophenyl)	H
CO(2-(trifluoromethyl)phenyl)	H
CO(isopropyl)	H
CO(tert-butyl)	H
CO(3-thiopheneyl)	H
CO(2-thiopheneyl)	H
CO(2,4,5-trifluorophenyl)	H
CO(2,5-difluorophenyl)	H
CO_2(phenyl)	H
SO_2(phenyl)	H
CO(2-chlorophenyl)	methyl
CO(2-(trifluoromethyl)phenyl)	methyl
CO(3-chlorophenyl)	methyl
CONH(phenyl)	H
CO(2,6-difluorophenyl)	H
$COCH_2$(2,4-difluorophenyl)	H
CO(2,4-difluorophenyl)	H
CO(2-fluorophenyl)	H
CO(2-(trifluoromethyl)-4-fluorophenyl)	*n*-propyl

Table I

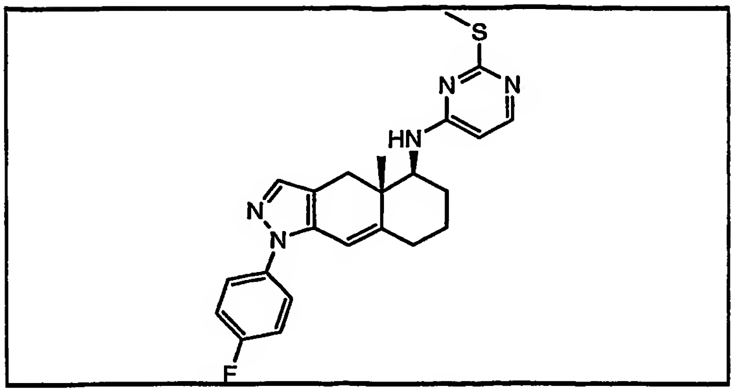
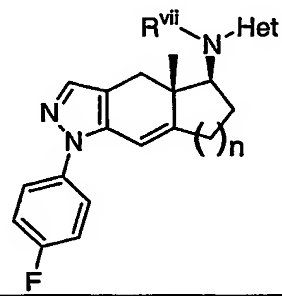


Table J



n	Het (Heterocycle)	R^{vii} Group
1	2-pyridyl	H
1	4-isoquinolyl	H
1	2-(4-methyl)pyridyl	H
1	5-pyrimidyl	H
1	3-pyridyl	H
1	2-pyrimidyl	H
1	2-pyrimidyl	methyl
1	2-pyrimidyl	*n*-propyl
1	4-(2-methylthio)pyrimidyl	H
2	4-(2-methylthio)pyrimidyl	methyl
2	4-(2-methylthio)pyrimidyl	*n*-propyl
1	2-(4-trifluoromethyl)pyridyl	H
2	2-(4-trifluoromethyl)pyridyl	H
1	2-pyrazinyl	H
1	4-(2,3,5,6-tetrafluoro)pyridyl	H
2	4-(2,3,5,6-tetrafluoro)pyridyl	H

Table K

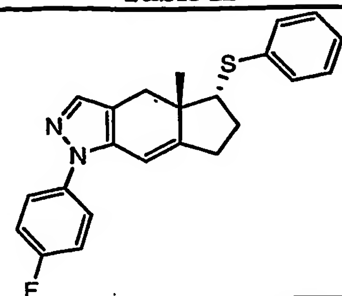
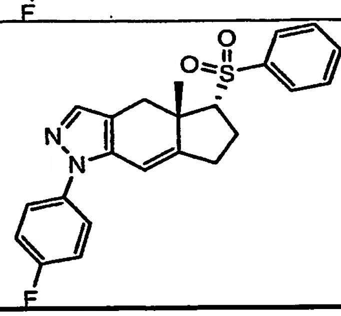
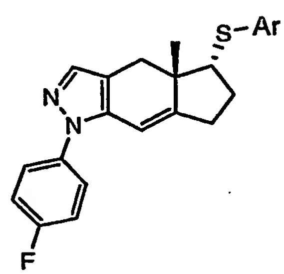



Table L



Ar Group
2-chlorophenyl
3-chlorophenyl

Ar Group
2-(trifluoromethyl)phenyl
2,6-dichlorophenyl
2,4-dichlorophenyl

or a pharmaceutically acceptable salt of any compound selected from any of the tables above.

18. A pharmaceutical composition comprising a compound according to Claim 1 in combination with a pharmaceutically acceptable carrier.

19. A method for treating a glucocorticoid receptor mediated disease or condition in a mammalian patient in need of such treatment comprising administering the patient a compound according to Claim 1 in an amount that is effective for treating the glucocorticoid receptor mediated disease or condition.

20. The method according to Claim 19 wherein the glucocorticoid receptor mediated disease or condition is selected from the group consisting of: tissue rejection, leukemias, lymphomas, Cushing's syndrome, acute adrenal insufficiency, congenital adrenal hyperplasia, rheumatic fever, polyarteritis nodosa, granulomatous polyarteritis, inhibition of myeloid cell lines, immune proliferation/apoptosis, HPA axis suppression and regulation, hypercortisolemia, stroke and spinal cord injury, hypercalcemia, hypergylcemia, acute adrenal insufficiency, chronic primary adrenal insufficiency, secondary adrenal insufficiency, congenital adrenal hyperplasia, cerebral edema, thrombocytopenia, Little's syndrome, obesity, metabolic syndrome, inflammatory bowel disease, systemic lupus erythematosus, polyartitis nodosa, Wegener's granulomatosis, giant cell arteritis, rheumatoid arthritis, juvenile rheumatoid arthritis, uveitis, hay fever, allergic rhinitis, urticaria, angioneurotic edema, chronic obstructive pulmonary disease, asthma, tendonitis, bursitis, Crohn's disease, ulcerative colitis, autoimmune chronic active hepatitis, organ transplantation, hepatitis, cirrhosis, inflammatory scalp alopecia, panniculitis, psoriasis, discoid lupus erythematosus, inflamed cysts, atopic dermatitis, pyoderma gangrenosum, pemphigus vulgaris, buflous pemphigoid, systemic lupus erythematosus, dermatomyositis, herpes gestationis, eosinophilic fasciitis, relapsing polychondritis, inflammatory vasculitis, sarcoidosis, Sweet's disease, type I reactive leprosy, capillary

hemangiomas, contact dermatitis, atopic dermatitis, lichen planus, exfoliative dermatitus, erythema nodosum, acne, hirsutism, toxic epidermal necrolysis, erythema multiform, cutaneous T-cell lymphoma, Human Immunodeficiency Virus (HIV), cell apoptosis, cancer, Kaposi's sarcoma, retinitis pigmentosa, cognitive performance, memory and learning enhancement, depression, addiction, mood disorders, chronic fatigue syndrome, schizophrenia, sleep disorders, and anxiety.

21. A method of selectively modulating the transactivation, transrepression, agonism and antagonism effects of the glucocorticoid receptor in a mammal comprising administering to the mammal a compound according to Claim 1 in an amount that is effective to modulate the glucocorticoid receptor.